Simplified approach

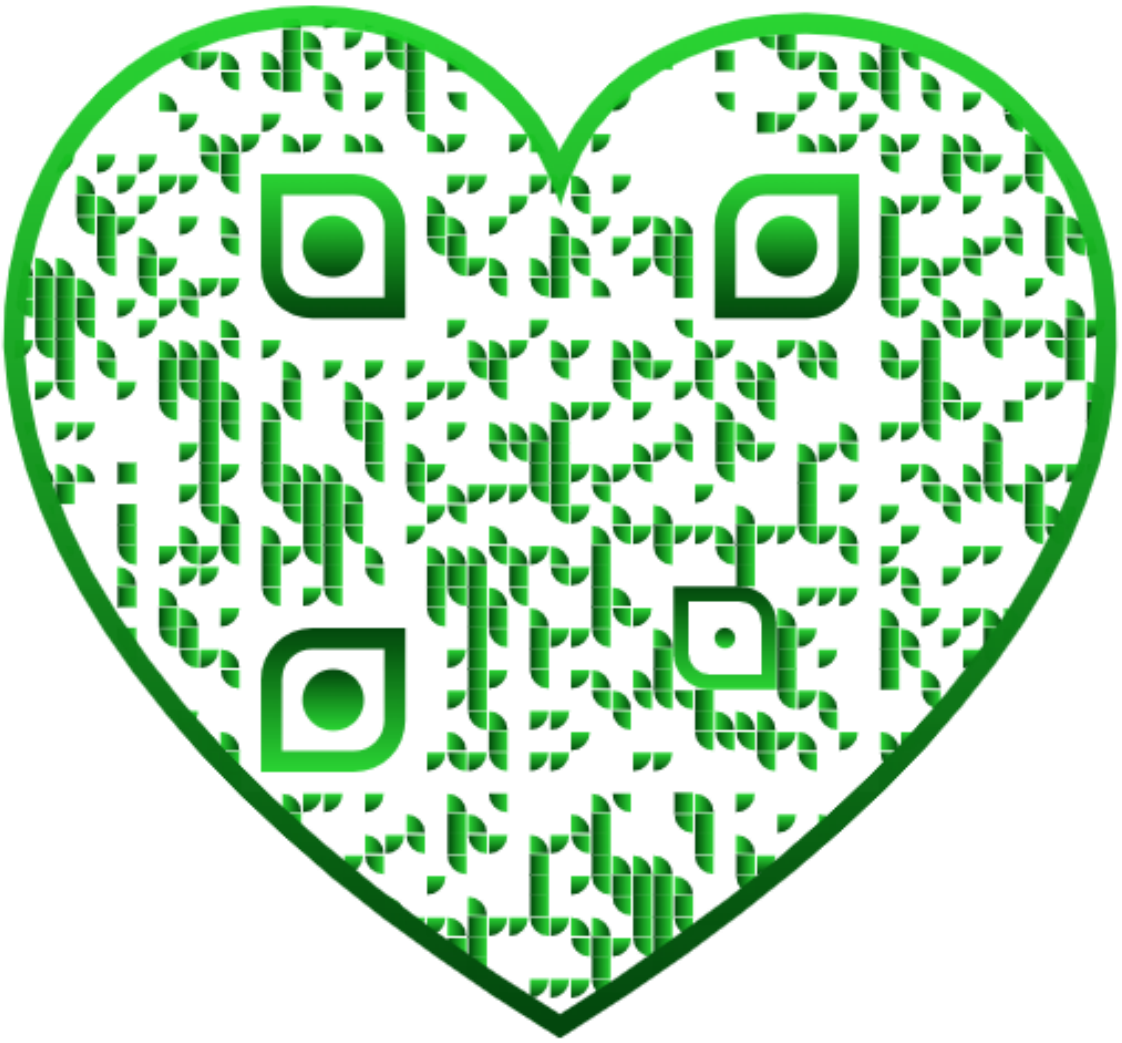
Mansoura Clinical Pharmacology

For Medical students

Edited by

Staff members of
Clinical Pharmacology Department
Faculty of Medicine
Mansoura University

Volume 3



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Preface

Clinical training for undergraduate students often focuses on diagnostic rather than therapeutic skills. Sometimes students are only expected to copy the prescribing behavior of their clinical teachers, or existing standard treatment guidelines, without explanation as to why certain treatment is chosen. Books may not be much help either. Pharmacology reference works and formularies are drug-centered, and although clinical textbooks and treatment guidelines are disease-centered and provide treatment recommendations, they rarely discuss why these therapies are chosen. Different sources may give contradictory advice.

This book in primarily intended for under graduate medical students who are about to enter the clinical phase of their studies. It will provide step by step guidance to the process of rational prescribing together with many illustrative examples. It teaches also skills that are necessary throughout a clinical career. Postgraduate students and practicing doctors may also find it a source of straightforward information.

I wish to acknowledge the ongoing efforts of my contributing authors, and we are deeply grateful to all those who have with such good grace given us their time and energy to supply valuable facts and opinions, they principally include:

- **Prof. Hussein El-Beltagi** who took over the preparation of all books since the 1st edition in 1995 including the revision process, printing control, distribution and selling control.
- **Assist. Prof. Mohamed-Hesham Daba** who took over the revision process and amendments of the last two editions.
- **Assist. Prof. Abdel-Motaal Fouda** who prepared the last two editions in a readable up-to-date text to provide essential information necessary throughout the clinical career.
- **Dr. Sameh Abdel-Ghany** who assisted in the revision process.

Much of any merit this book may have is due to the generosity of those named above.

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Mission and Vision

Our mission

The Clinical Pharmacology Department is seeking excellence and leadership in four major core activities: education, research, community service, and faculty and staff development. We are connecting basic medical sciences with clinical care through innovative and disciplined teaching of clinical pharmacology in an integrative manner

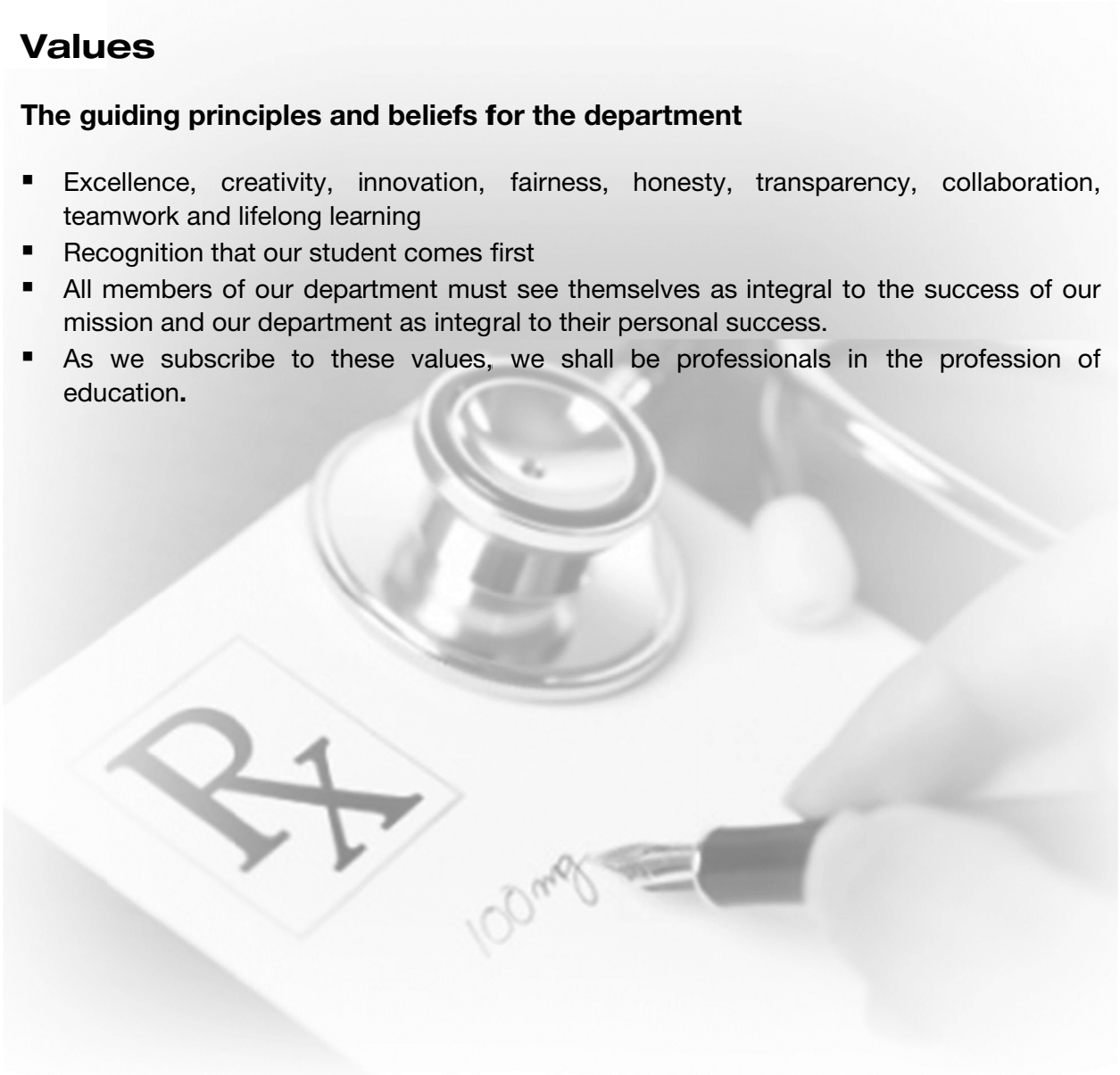
Our vision

The department of Clinical Pharmacology is aiming to be a premier academic model in the field of pharmacology and therapeutics in Egypt and Middle East through promoting use of the best therapeutics and developing newer experimental and clinical research projects.

Values

The guiding principles and beliefs for the department

- Excellence, creativity, innovation, fairness, honesty, transparency, collaboration, teamwork and lifelong learning
- Recognition that our student comes first
- All members of our department must see themselves as integral to the success of our mission and our department as integral to their personal success.
- As we subscribe to these values, we shall be professionals in the profession of education.



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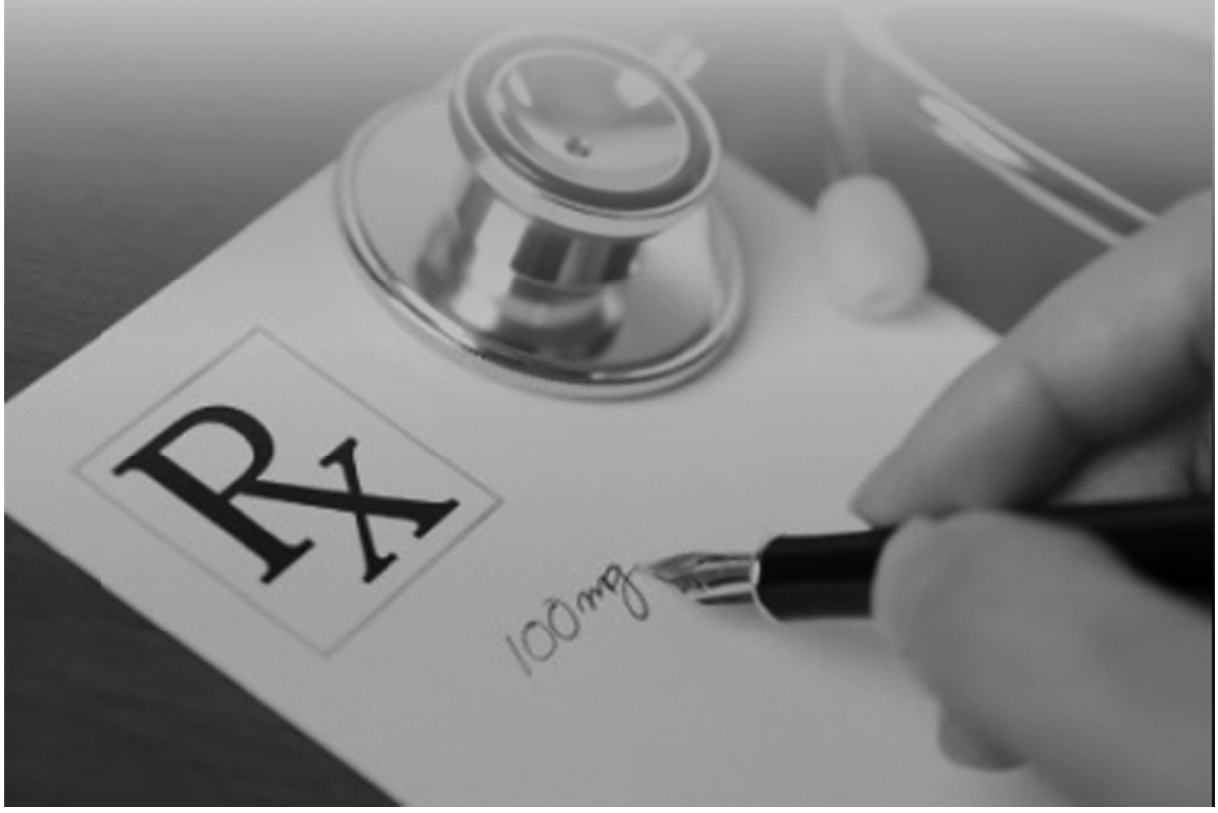
Chapter 8

Gastrointestinal Pharmacology



Chapter 8
Gastrointestinal Pharmacology

Part 1: Peptic Ulcer Disease and Reflux Esophagitis

PEPTIC ULCER

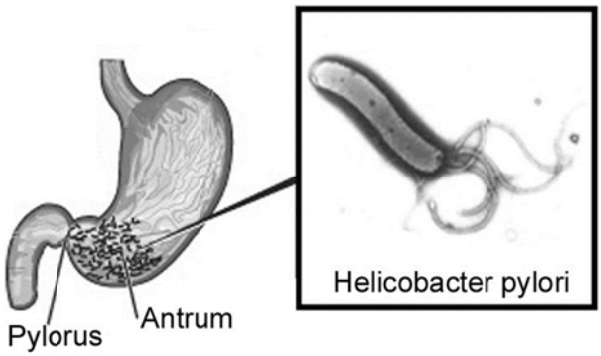
Definition: ulceration of the duodenum or stomach due to imbalance between local invasive force (e.g. HCl and pepsin) and protective mechanisms.

Invasive factors:

- Stress: ↑ HCl and pepsin secretion by parietal cells.
- Diet: coffee, alcohol and spices.
- **Drugs:** NSAIDs, corticosteroids, morphine, methylxanthines, etc.
- **Infection** with ***Helicobacter pylori.***
  H. pylori is spiral gram –ve flagellates found in the antrum of human stomach. Certain enzymes and toxins produced by the bacteria cause tissue damage. Infection with *H. pylori* can be diagnosed by endoscopic biopsy or serological markers.

Defensive mechanisms:

- Mucus production by gastric mucosa.
- Pancreatic bicarbonate secretion.
- Good mucosal blood flow.
- Local PGE_2 and PGI_2 production.

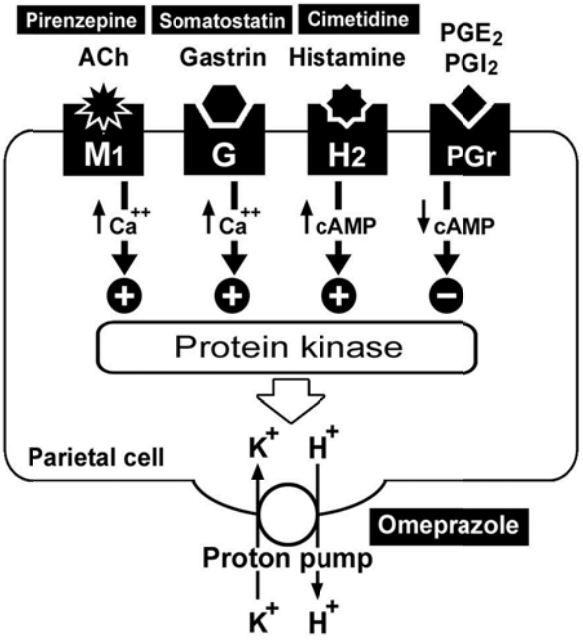


Regulation of HCl secretion

- **Ach:** ↑ HCl secretion through $\mathbf{M_1}$ receptors → ↑ intracellular Ca^{2+}.
- **Gastrin:** ↑ HCl secretion through **G** receptors → ↑ intracellular Ca^{2+}.
- **Histamine:** ↑ HCl secretion through $\mathbf{H_2}$ receptors → ↑ intracellular cAMP.

Both Ca^{2+} and cAMP activate H^+/K^+ *ATPase* at the membrane of the parietal cell to secrete H^+ into the gastric lumen **"proton pump"**.

- **PGE_2** and **PGI_2:** act on PG receptors → ↓ cAMP → ↓ HCl secretion.

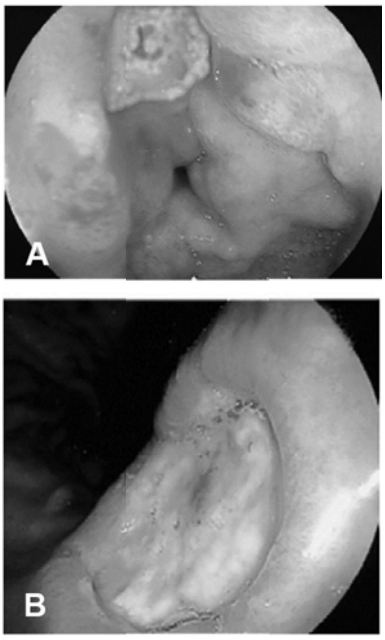


Clinical picture

- Epigastric pain: characterized by:
  - Diffuse and worsens by food in **GU.**
  - Localized (point tenderness) and relieved by food in **DU.**
- Signs of complications e.g. bleeding, anemia, etc.

Diagnosis

- Endoscopy: visualization of the ulcer.
- Radiologic: by barium meal.



Endoscopic views. (a) Duodenal ulcer with inflamed duodenal .folds. (b) Benign gastric ulcer

Therapy of peptic ulcer

Non-drug therapy = life style modification

- Rest and **S**edation: they improve healing and relief pain of DU.
- Stop **S**moking, **S**pices, alcohol, coffee, and tea: because they ↑ HCl.
- Avoid **S**tress: because stress ↑ HCl.
- Avoid ulcerogenic drugs: e.g. NSAIDs.
- Diet:
  - Frequent small meals in DU in order to buffer high acidity.
  - Encourage milk and fats.
  - Avoid **S**pices and fried food

Pharmacological therapy

- **Drugs that neutralize HCl:** antacids

- **Drugs that ↓ HCl secretion:**

- Selective M_1 blockers: pirenzepine, telenzepine.
- H_2 blockers: cimetidine, ranitidine, famotidine.
- Proton pump inhibitors: omeprazole, lanzoprazole, etc.

- **Drugs that ↑ mucosal defense mechanisms:**
  - Sucralfate
  - Colloid bismuth compounds: e.g. bismuth subcitrate.
  - Carbenoxolone
  - PGE_1 analogues: misoprostol.

- **Antimicrobial drugs** for *H. pylori*: see later.

- **Adjuvant therapy:** Sedatives and multivitamins to ↓ stress to enhance healing.

ANTACIDS

- Antacids are weak bases that are taken orally and partially neutralize gastric acid and reduce pepsin activity.
- They are used as **symptomatic relief** of hyperacidity and should **not** be used as long-term treatment.

Sodium bicarbonate	Calcium carbonate	Magnesium and aluminum salts (Mg hydroxide and Aluminium hydroxide)
▪ It can be **absorbed** systemically leading to salt & water retention, and metabolic alkalosis. ▪ It is contraindicated in hypertension and heart failure. ▪ It has **rapid** onset and short duration.	▪ **Partially** absorbed antacid. ▪ Ca^{2+} may act directly to stimulate gastrin secretion leading to acid rebound. ▪ It is contraindicated in hypercalcemia and renal stones.	▪ They are **poorly** absorbed from GIT and have no systemic effects. ▪ The unabsorbed Mg salts cause osmotic **diarrhea**; the unabsorbed Al salts cause **constipation**. ▪ They have **slow** onset.

Adverse effects

- **Change in bowel habits:** Al^{3+} hydroxide causes *constipation*, while Mg^{2+} hydroxide cause *diarrhea*. For this reason, both salts are combined together to manage this problem.

- **Rebound hyperacidity:** with Ca^{2+} and $NaHCO_3$ containing antacids.
- **Cation overload:**
  - Na^+ salts → hypertension and systemic alkalosis.
  - Ca^{2+} salts → hypercalcemia, renal stones and **milk-alkali syndrome.**

Milk-alkali syndrome

Patients with PU usually administer large amounts of milk and antacids to relieve symptoms of hyperacidity.

- Excess milk ⟶ hypercalcemia.
- Excess antacids ⟶ alkalosis (due to continuous wash of HCl).

- **Decrease absorption of other drugs:** the metal ion in some preparations can chelate other drugs especially tetracycline, digitalis and iron.

N.B. when **iron** or **tetracycline** is prescribed with antacids, we should make **30 min** interval between both drugs to avoid **chelation** with the antacid.

DECREASE HCL SECRETION

1. Selective M_1 blockers:

(Pirenzepine - Telenzepine)

Mechanism of action: selectively block gastric M_1 receptors → ↓ **basal** HCl secretion.

Uses: The selective M_1 blockers are **weak** inhibitors of HCl secretion and are now replaced by more effective drugs. They are sometimes used as adjuvant therapy with H_2 blockers.

Adverse effects: high doses produce atropine-like effects: dry mouth, blurred vision, tachycardia, urine retention.

N.B. Atropine itself is not used in the treatment of PU because it is non-selective M blocker and **may aggravate esophageal reflux.**

2. H2 blockers:

(Cimetidine – Ranitidine – Famotidine - Nizatidine)

Mechanism and pharmacological effects

- They act as competitive inhibitors of histamine H2-receptors on the parietal cell. This results in a marked ↓ in histamine-stimulated HCl secretion.
- Although other agents such as gastrin and ACh may induce acid secretion, histamine is the predominant final mediator that stimulates HCl secretion.

Therapeutic uses

- Duodenal and gastric ulcers.
- Prophylaxis & treatment of stress ulcers (e.g. after burn or major trauma).
- Prophylaxis against bleeding of esophageal varices.
- Reflux esophagitis.
- Zollinger-Ellison syndrome (gastrin-secreting tumor of the pancreas which ↑ HCl secretion): usually larger doses are required.
- With ulcerogenic drugs (e.g. NSAIDs) to protect the gastric mucosa from injury.

Adverse effects (mostly with cimetidine):

- **Cimetidine** has **anti-androgenic effects** (due to block of androgen receptors) leading to ↓ sperm count, impotence and gynecomastia.
- **Cimetidine** inhibits **hepatic microsomal enzymes (P450)** leading to ↓ metabolism of other drugs e.g. theophylline, warfarin, sulphonylureas, etc.
- **R**eversible hepatotoxicity and **R**eversible anemia.
- **CNS** symptoms: headache, slurred speech, delirium, coma, etc. occurs mainly in **elderly people** with **i.v.** administration.

Precautions of H2 blockers

- Avoid sudden withdrawal to prevent rebound ulceration.
- Avoid their use in pregnancy and lactation (they cross the placental barrier and secreted in breast milk).
- Avoid combination of cimetidine with drugs having narrow therapeutic index (because cimetidine inhibits microsomal P450 and ↑ their toxicity).

	Cimetidine	Ranitidine	Famotidine
H_2 Blocking effect:	Weak	Potent	More potent
Anti-anderogenic effect:	Strong	Minimal	No
Liver enzyme inhibition	Strong	Minimal	No
Adverse CNS effects:	Frequent	Less frequent	Less frequent
Duration of action:	8 h	12 h	24 h
Dose:	**800** mg/day for 6-8 weeks then **400** mg/day for 6-8 months	**300** mg/day for 6-8 weeks then **150** mg/day for 6-8 months	**20** mg/day for 6-8 weeks then **10** mg/day for 6-8 months

3. Proton pump inhibitors (PPIs):

(Omeprazole – Lansoprazole – Pantoprazole)

Chemistry: all are imidazole derivatives.

▶ **Imidazole derivatives:**

1. **Nasal decongestants:** Nafazoline
2. **Antimicrobials:** Metronidazole
3. **Antifungal:** Ketoconazole
4. **Antiparasitic:** Mebendazole
5. **Proton pump inhibitors:** Omeprazole

Mechanism of action

- They are **prodrugs**. They are converted into the active form in the gastric mucosa and produce **irreversible inhibition** of gastric H^+/K^+ *ATPase* enzyme leading to ↓ both **basal** and **stimulated** HCl secretion to around the **zero** level for 1-2 days.
- Full restoration of acid secretion after stopping the PPI takes about 3-5 days (time of re-synthesis of H^+/K^+ *ATPase*).
- Their bioavailability is decreased significantly by food and, ideally, should be administered 1 hour before a meal.

Therapeutic uses: The same as H_2 blockers **(dose of omeprazole: 20-40** mg/day orally for 4-6 weeks then **10-20** mg/day for 4-6 months to prevent recurrence).

Adverse effects

- Low incidence of diarrhea, abdominal colic, dizziness, skin rash, **leucopenia**, and transient increase of liver enzymes.
- **Decrease vit B_{12} absorption** after > 12 weeks of therapy due to interference with intrinsic factor secretion by the stomach.
- Inhibition of gastric acidity leads to **alteration of bioavialability of some drugs** e.g. ketoconazole, digoxin, and iron.
- Omeprazole **inhibits microsomal P450 enzymes** and decreases metabolism of phenytoin, warfarin, and cyclosporin. Newer PPIs do **not** affect liver enzymes.
- Omeprazole in high dose induced gastric **carcinoid tumor** in rats.

ENHANCING MUCOSAL DEFENSE MECHANISMS

1. Sucralfate

- It is an aluminum salt of sulfated sucrose.
- Slightly (3%) absorbed from the GIT. The aluminum metal may accumulate in cases of renal failure, so it should be avoided in **renal failure**.

Mechanism of action

- It **needs acidic medium** to be activated. In the presence of acidic medium, it

forms a complex with protein debris at the ulcer base and forms a physical barrier (so **not** taken with antacids, H_2 blockers, or PPIs).
- It ↓ pepsin secretion and ↑ secretion of endogenous PGs.

Adverse effects

– Constipation (due to presence of aluminum).
– ↓↓ absorption of tetracycline, digoxin and phenytoin.

N.B. Both sucralfate and bismuth compound are **not given** simultaneously with antacids or H_2 blockers (at least **30** min must be elapsed in-between). **Why?**

2. Bismuth compounds:
Bismuth subsalicylate and subcitrate

Mechanism of action

- In acidic pH, it forms a complex with protein debris at the ulcer base and forms a physical barrier.
- It ↓ pepsin secretion and ↑ secretion of endogenous PGs.
- It has **additional antimicrobial activity** against *H. pylori.*

Adverse effects

– Stool and teeth discoloration.
– **Encephalopathy** in presence of **renal failure**

Contraindications: Chronic renal failure and CNS diseases.

3. Carbenoxolone

It is a *liquorice* derivative having **steroid** structure.

Mechanism of action

- It ↑ production and viscosity of gastric mucus and ↑ mucosal resistance.
- It ↓ pepsin secretion and ↑ secretion of endogenous PGs.

Adverse effects

Salt & water retention (aldosterone-like effects) → edema and hypertension especially in cardiac and renal patients. This edema can be treated by thiazide diuretics (**not by spironolactone)** because both spironolactone and carbenoxolone have steroid structure and can compete with each other.

Contraindications: Hypertension and/or renal failure

4. Synthetic PGE1 analogue: Misoprostol

Mechanism of action

- It acts on specific receptors on gastric parietal cells to ↓ histamine-stimulated HCl secretion.
- ↑ mucus and bicarbonate secretion (cytoprotective action).
- ↑ mucosal blood flow and stimulates mucosal cellular regeneration.

Therapeutic uses

Prevention of peptic ulcer in high risk patients e.g. those on long term use of NSAIDs for chronic inflammatory diseases. [**misoprostol** 200 μg is combined with **naproxen** or **diclofenac** in single tablet].

Adverse effects

- Diarrhea and cramping pain: due to ↑ GIT motility and water secretion.
- Uterine contractions during pregnancy → **abortion**.

Contraindications: pregnancy.

ERADICATION THERAPY FOR *H. pylori*

- Infection with *H. pylori* is a **main cause of recurrence** of PU.
- The following 10 days ***"sequential protocol"*** is highly effective for eradication of *H. pylori*:

PPIs
Amoxicillin 1 g] twice daily for 5 days (days 1-5).

PPIs
Clarithromycin 500 mg
Tinidazole 500 mg] twice daily for 5 days (days 6-10).

THERAPY OF BLEEDING PEPTIC ULCER

- **Hospitalization** and **Fresh blood transfusion**.
- **Acid suppression with high dose PPIs** by continuous i.v. infusion is the standard of care e.g. omeprazole 80 mg i.v. bolus followed by 8 mg/h for 72h.
- **Vitamin K_1:** 10 mg i.m or s.c.
- **Endoscopic therapy:** several types of endoscopic treatments are available.

TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Definition: reflux of gastric contents into the esophagus due to incompetent lower esophageal sphincter (LES). **Heartburn** and chest pain are the major complain which may be misdiagnosed of angina pectoris.

Non-drug therapy = life style modification

- **Head of bed elevation:** because most damage to the esophagus occurs at night when HCl can remain in contact with the mucosa for long period.
- **Weight reduction.**
- **Avoid:**
  - **S**tress, **S**moking, **S**pices, alcohol.
  - Ulcerogenic **drugs** e.g. NSAIDs.

Drugs ↑ LES pressure:

- Metoclopramide
- Domperidone
- Bethanechol
- Erythromycin

Drugs ↓ LES pressure:

- Anticholinergic drugs
- Nitrates

Drug therapy

- Decreasing HCl secretion: H_2 blockers and proton pump inhibitors.
- Prokinetic drugs.
- Antacids and antacid combinations: (Gaviscon).

Surgical treatment: if medical therapy failed.

PROKINETIC DRUGS

Definition: they are drugs that increase **upper GIT motility** and enhance gastric emptying. They include:

- **Dopamine antagonists:** e.g. Metoclopramide and Domperidone.
- **Serotonin (5-HT4)** agonists: e.g. Mosapride
- **Cholinomimetic agents:** e.g. Bethanechol.
- **Macrolide antibiotics:** e.g. Erythromycin

1. Metoclopramide

Mechanism and pharmacological effects

- Metoclopramide ↑ LES tone and enhances gastric emptying and **upper** GIT motility through:
  - Blocking of dopamine (D) receptors (central & peripheral) leading to decrease the inhibitory action of dopamine on the GIT motility.
  - Enhances cholinergic transmission in the upper GIT.

- **N.B.** Metoclopramide has **no effect** on small intestinal or colonic motility.

- **Antiemetic action:** due to blockade of D2 receptors in the chemoreceptor trigger zone of the medulla (**CTZ).**

Therapeutic uses

- **Gastroesophageal reflux:** to enhance gastric emptying and ↑ LES pressure.
- **Disorders of gastric emptying**: e.g. diabetic gastroparesis and postoperative gastric retention.
- **Before small bowel endoscopy** (20 mg given by slow i.v.i.): to enhance gastric evacuation and peristaltic movement. Also to prevent vomiting.
- **Before emergency surgery** and labor to evacuate the stomach and prevent aspiration of gastric contents during anesthesia.
- **Treatment of nausea and vomiting** of various causes.

Adverse effects

- Sedation (the most common adverse effect).
- **Extrapyramidal effects** (e.g. *dystonia* and *dyskinesia*): (especially in **old age**) due to blockade of D_2 in the *basal ganglia*.
- **Hyperprolactinemia** due to blockade of D_2 in the *pituitary gland*.

Drug interactions

- **Anticholinergic drugs (e.g. atropine)** antagonize its prokinetic action.
- **Other dopamine blockers** (e.g. antipsychotic drugs) administered with metoclopramide may precipitate acute extrapyramidal effects.

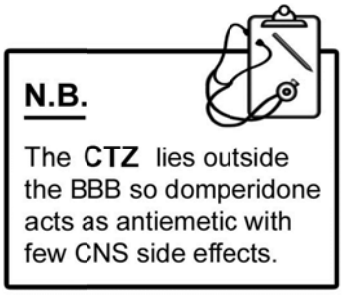
2. Domperidone

Mechanism and pharmacological effects

- **It blocks peripheral D_2 receptors leading to** ↓ the inhibitory action of dopamine on GIT motility. It does **NOT** cross BBB so it has no CNS side effects.
- **Antiemetic effect** less than metoclopramide.

Therapeutic uses

- The same uses as metoclopramide.
- To counteract nausea and vomiting caused by **levodopa** and **bromocriptine** during treatment of **Parkinson's disease** because it blocks D2 receptors in the CTZ responsible for vomiting but does **not** block D2 receptors in the basal ganglia responsible for parkinsonism.



Adverse effects: there is growing evidence that domperidone may ↑ QT interval and predispose to serious arrhythmia and sudden death.

	Metoclopramide	Domperidone
Dopamine receptor blockade	Central and peripheral	Peripheral only
Cholinergic transmission	Increase	No effect
Antiemetic effect	Strong	Weaker
Extra-pyramidal side effects	Present	No
Hyperprolactinemia	Significant	Minimal

3. Bethanechol

Bethanechol stimulates muscarinic M3 in the smooth ms of the GIT and myenteric plexus. It was used in the past for the treatment of GERD and gastroparesis, but now, it is rarely used for this indication due to multiple cholinergic side effects.

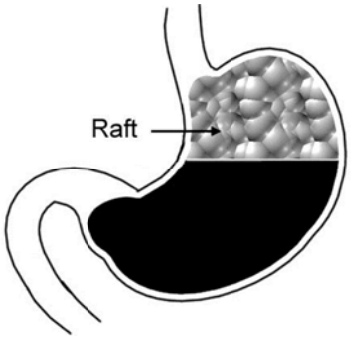
4. Macrolide antibiotics: erythromycin

Macrolide antibiotics such as erythromycin directly stimulate **motilin receptors** on GIT smooth muscle and promote the onset of a migrating motor complex. Intravenous erythromycin (3 mg/kg) is beneficial in some patients with gastroparesis; however, tolerance rapidly develops. It may be used in patients with acute upper GIT hemorrhage to promote gastric emptying of blood before endoscopy.

ANTACIDS AND ANTACID-ALGINIC ACID PRODUCTS

Gaviscon: (alginic acid + Mg-trisilicate + Al-hydroxide + $NaHCO_3$):

Alginic acid in presence of saliva and $NaHCO_3$ forms a highly viscous foamy solution of Na-alginate that floats on the gastric contents as a **raft** and prevents gastric reflux.



H2 BLOCKERS AND PPIS

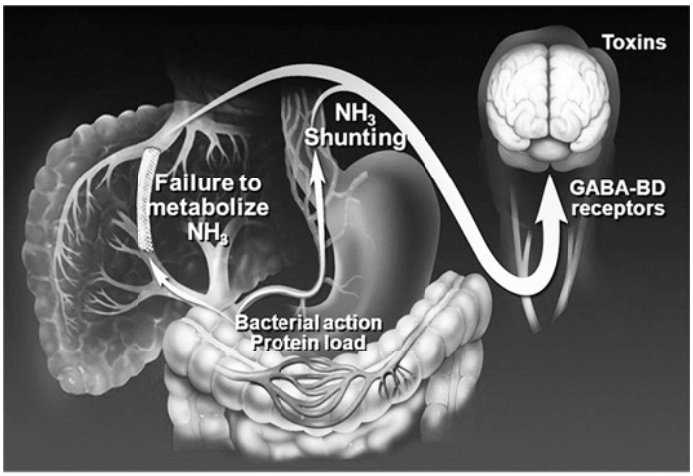
- PPIs are **more effective** than H2 blockers for the treatment of GERD.
- Once-daily dosing of PPIs provides effective symptom relief and tissue healing in 85–90% of patients; up to 15% of patients require twice-daily dosing.

Part 2: Management of Liver Disease Complications

MANAGEMENT OF HEPATIC ENCEPHALOPATHY

Definition and pathogenesis

Hepatic encephalopathy is the syndrome of disordered consciousness and neuromuscular activity seen in patients with acute or chronic liver failure.



Pathogenesis of portosystemic encephalopathy

The failing liver cannot metabolize **ammonia** and **benzodiazepines-like mediators (GABA-like transmitters)** generated by the intestinal bacteria. These toxins are shunted directly to the CNS causing encephalopathy.

Management: Treatment is aimed at **reduction of hyperammonemia:**

- **Diet:**
  - **Protein restriction** to decrease formation of ammonia by intestinal bacteria.
  - **Vegetable** protein is better tolerated than animal protein.
  - The rationale and benefit of dietary protein restriction is **controversial**.

- **Enemas**: cleansing of the colon is a rapid and effective method to remove ammoniagenic substrates. It can be done with lactulose or tape water.

- **Lactulose:**
  - It is synthetic non-absorbable disaccharide. In the colon, it is transformed by bacteria into **lactic** and **acetic** acids → ↓ pH of the colonic medium **leading to:**
    - Inhibition of intestinal bacteria → ↓ production of ammonia.
    - ↑ transport of ammonia from blood to intestinal lumen where it is converted to the poorly absorbed ammonium ion.
    - Osmotic laxation → ↑ excretion of ammonium ion.
  - It is administered orally or as enema (for patients in coma).
  - **Adverse effects:** relatively safe drug.

- **Oral antibiotics:**

  Neomycin:
  - It is non-absorbable aminoglycoside antibiotic.

- It ↓ blood ammonia by killing intestinal bacteria that generate ammonia.
- It is used in a dose of 1-2 g 4 times daily orally or as retention enema.
- Small amounts of neomycin may be absorbed (~1%) and result in ototoxicity and nephrotoxicity especially in patients with renal impairment.

Other antibiotics:

- **Metronidazole** acts on anaerobic bacteria. It is the preferred option if there is fear from adverse effects of neomycin (but given for short term).
- **Rifaximin:** is non-absorbable and better tolerated antibiotic.

MANAGEMENT OF VARICEAL BLEEDING DUE TO PORTAL HYPERTENSION

Management of acute bleeding

- **Fresh blood transfusion.**
- **Acid suppression** with **omeprazole** (80 mg) to minimize HCl irritation.
- **i.v. vasopressin or its analogues:**
  - **Vasopressin:**
    - It produces mesenteric VC leading to ↓ portal venous flow and pressure.
    - It can produce systemic VC (coronary, cerebral, limb, etc), so it is better combined with i.v. **nitroglycerine** to reduce systemic and coronary VC.
    - The vasopressin/nitroglycerine combination is **rarely** used now.
  - **Terlipressin:**
    - It is synthetic analog of vasopressin that is released in a slow and sustained manner allowing more sustained hemodynamic effects with fewer systemic side effects than vasopressin.
- **Prophylactic antibiotics:** to prevent infectious complications after GI hemorrhage. The preferred antibiotic is **i.v. ceftriaxone** 1 gm/day for 7 days.
- **Endoscopic sclerotherapy:** injection of the varices with a sclerosing agent to induce fibrosis and obliteration.

Prevention of re-bleeding (prophylaxis):

- **Beta-blockers (propranolol** 40 mg twice daily). It ↓ portal BP through:
  - They ↓ COP → ↓ portal blood flow.
  - They cause unopposed α- action → VC of the splanchnic vascular bed.
- **H_2 blockers or PPIs:** to prevent gastroduodenal erosions.
- **Metoclopramide:** to enhance gastric evacuation and ↑ LES pressure.

Part 3: Antiemetic Drugs

Several classes of antiemetic drugs are available that antagonize the neurotransmitter receptors known to be involved in the physiology of nausea and vomiting. The antiemetic drugs are classified according to their primary action; some agents affect multiple receptors.

Drug	Antiemetic mechanism	Uses as antiemetic	Adverse effects
1. Muscarinic blockers: ▪ Atropine ▪ Hyoscine	They block **M_1** receptors in the vestibulocerebellar pathway, solitary tract nucleus, and chemoreceptor trigger zone (CTZ).	Prevention and treatment of vomiting due to **motion sickness** (0.3-0.6 mg/8 hrs orally).	– Blurred vision – Dry mouth – Urine retention – Glaucoma – Tachycardia
2. H1-blockers: ▪ Diphenhydramine ▪ Cyproheptadine ▪ Cyclizine ▪ Meclizine	– They block H_1 (also M_1) receptors in the vestibulo-cerebellar pathway and CTZ. – They have sedative action.	– Vomiting due to **motion sickness** (diphenhydramine) – Vomiting of **pregnancy** (cyclizine and meclizine) – **True vertigo**: combined with VDs to improve labyrinthine blood flow.	– Sedation (excitation may occur in children). – Atropine-like actions (dry mouth, blurred vision, urine retention). – Hypotension
3. 5-HT3 blockers: ▪ Ondansetron ▪ Granisetron ▪ Tropisetron	They block $5HT_3$ receptors in the GIT, solitary tract nucleus and CTZ.	– Vomiting due to **cancer chemotherapy** or **radio-therapy.** – **Postoperative** nausea and vomiting.	– Dizziness, headache, and constipation.
4. Dopamine blockers ▪ Metoclopramide	– They block D2 receptors in the CTZ.	– Vomiting due to **drugs** or fevers.	– Sedation – Extrapyramidal effects e.g.

▪ Domperidone ▪ Phenothiazines e.g. chlorpromazine	– They inhibit peripheral transmission to VC.	– Vomiting due to **cancer chemotherapy**. – **Postoperative** nausea and vomiting.	dystonia and dyskinesia. – Hyperprolactinemia – Postural hypotension
5. Cannabinoid derivatives: ▪ Nabilone and Dronabinol	– It is a partial agonist at central and peripheral cannabinoid receptors (CB1). The exact mechanism is unclear.	– Vomiting due to **cancer chemotherapy** – Patients refractory to other antiemetics.	– Sedation – Hallucinations – Psychotropic effects – Postural hypotension – Drug abuse.
6. Vitamin B6 (pyridoxin)	May be related to the balance between GABA (CNS *inhibitory* transmitter) and glutamate (CNS *excitatory* transmitter).	– Vomiting in **pregnancy** (50 mg at bedtime). – Vomiting in **children**	-
7. Corticosteroids ▪ Dexamethasone ▪ Prednisolone	The exact mechanism is unclear.	– Combined with Vit B6 to treat vomiting in **pregnancy**. – Vomiting due to **cancer chemotherapy**.	– See endocrine chapter
8. Benzodiazepines ▪ Lorazepam ▪ Diazepam	Allosteric facilitation of central GABA inhibitory transmission	– **Stress-related** vomiting – To controls symptoms in **Ménière disease**	– See CNS chapter
9. Neurokinin-1 receptor blockers: ▪ Aprepitant	Substance-P induces vomiting through stimulation of NK-1 receptors. Aprepitant blocks this receptor.	– In combination with 5-HT3 blockers to treat vomiting due to **cancer chemotherapy**	– Diarrhea and fatigue

Part 4: Antispasmodic Drugs (smooth ms relaxants)

Classification

- **Anticholinergic drugs:** atropine, hyoscine, propantheline, oxyphenonium.
- **Direct smooth muscle relaxants:** papaverine, mebeverine, alverine, drotaverine.
- **Mixtures:** Librax (clidinium + chlordiazepoxide), Donnatal (hyoscine + phenobarbital).

<table>
<tr><th></th><th>Papaverine</th><th>Mebeverine, Alverine, Drotaverine</th><th>Librax</th></tr>
<tr><td rowspan="2">Chemistry & mechanism of action</td><td>It is opium alkaloid but chemically different from morphine</td><td>They are synthetic drugs</td><td rowspan="2">It is a combination of:
▪ Chlordiazepoxide: benzodiazepine that has antianxiety effect.
▪ Clidinium: anticholinergic drug which ↓ GIT motility and spasm</td></tr>
<tr><td colspan="2">The exact mechanism is unclear but may be due to inhibition of PDE enzyme →↑ cAMP → smooth muscle relaxation.</td></tr>
<tr><td>Use</td><td colspan="3">▪ Spasms of the GIT, bile duct and genitourinary tract.
▪ Librax is used for treatment of irritable bowel syndrome (IBS).</td></tr>
<tr><td>Side effects</td><td colspan="2">– Cardiac arrhythmia.
– Abnormal liver functions in the form of elevated serum transaminases and alkaline phosphatase.
– Headache and dizziness</td><td>– Atropine-like actions e.g, dry mouth, urine retention, etc.
– Sedation, drowsiness, confusion, etc.</td></tr>
<tr><td>C/I</td><td colspan="3">– Paralytic ileus.
– Constipation for more than one week</td></tr>
</table>

Part 5: Therapy of Constipation

Non-drug therapy: It is the **first line** in all cases of constipation

- **Diet rich in fibers** e.g. fruits, vegetables, whole meal bread, etc. to be increased to 30 g/day.
- Increase **fluid intake**
- Minimize **tea** and coffee.
- Physical **exercise** to activate abdominal muscles and intestinal peristalsis. This help food move more efficiently through the gut.

Drug therapy: LAXATIVES:

Drug causes of constipation:

- **A**tropine and related drugs.
- **A**luminum containing antacids
- **A**dsorbents (kaolin & pectin).
- **CCBs:** e.g. **V**erapamil
- **Opioids:** morphine & loperamide

1. Bulk-forming agents:

[Dietary fibers – Methylcellulose – Bran]

Mechanism of action

They are non-digestible fibers; they retain water in the gut and distend the large intestine → activation of stretch receptors → stimulation of peristalsis.

Adverse effects: they are **safe** laxatives but may cause:

- Bloating and abdominal distension.
- ↓ absorption of some drugs e.g. digoxin.
- They may form masses in the gut leading to intestinal obstruction.

2. Osmotic laxatives:

[Mg sulfate & Na salts – Lactulose – Polyethylene glycol]

Mechanism of action

They are retained in the gut lumen and retain water by their osmotic effect → activation of stretch receptors → stimulation of peristalsis.

Adverse effects

- Mg & Na salts (saline laxatives) may be absorbed systemically and produce *hypermagnesemia* and *hypernatremia* especially in patients with renal failure.
- Lactulose may produce abdominal discomfort.
- Polyethylene glycol may produce electrolyte disturbance (hypokalemia).

3. Irritant (or stimulant) laxatives:

[Castor oil – Senna – Bisacodyl]

Mechanism of action

They produce inflammation (irritation) of the intestinal mucosa and inhibit Na^+/K^+ *ATPase enzyme* leading to:

- Accumulation of water and electrolytes in the gut lumen.
- Direct stimulation of peristalsis by their irritant effect.

Adverse effects

Castor oil
- Bad taste.
- Stimulation of uterine contraction and **abortion**

Senna
- It passes in urine and cause **urine discoloration**
- It passes in breast milk and cause **cathartic** effect in the baby.
- Prolonged use → degeneration of gut nervous plexus → **atonic** (cathartic) colon.
- Increase menstrual blood flow and **abortion** in pregnancy.
- **Laxative dependence:** Irritant laxatives cause complete evacuation of the colon. The colon requires 2-5 days before the normal fecal mass can be reestablished. The patient becomes worry regarding the lack of bowel movement during this period and may use the laxative again and a vicious cycle is established leading to partial or complete loss of normal bowel function.

Bisacodyl
- It is prepared as enteric coated tablets to avoid gastric irritation. If it is given with milk or with other drugs that change gastric pH, the enteric coating may dissolve in the stomach and cause gastric irritation and pain
- Prolonged use → degeneration of gut nervous plexus → **atonic** (cathartic) colon *(should not be used more than 10 days).*

4. Stool softeners: Docusate sodium

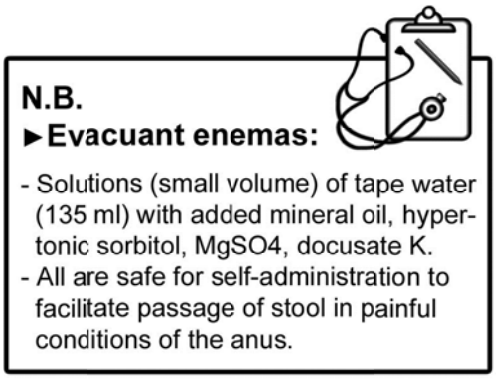
Mechanism: they are anionic surfactants that enable additional water and fats to be incorporated in the stool, making it easier to move through the GIT.

5. Lubricant laxatives:

[Liquid paraffin – Glycerin suppositories – Evacuant enema]

Mechanism of action

- **Paraffin oil** it coats the fecal matter and retards water absorption by the colon.
- **Glycerin** has hygroscopic effect. It draws water from rectal mucosa and lubricates the anal canal. It also stimulates reflex rectal contractions and promotes stool evacuation in 15-20 min.


N.B.
►Evacuant enemas:
- Solutions (small volume) of tape water (135 ml) with added mineral oil, hyper-tonic sorbitol, MgSO4, docusate K.
- All are safe for self-administration to facilitate passage of stool in painful conditions of the anus.

Adverse effects: paraffin oil decreases absorption of fat-soluble vitamins

6. Chloride channel activators: Lubiprostone

Mechanism of action

It acts by activating chloride channels to increase fluid secretion in the intestinal lumen. This eases the passage of stool and causes little change in electrolyte balance.

General indications of laxatives

- **Constipation:** laxatives should not be used for prolonged duration to avoid laxative dependence.
- To fasten excretion of **toxic** substances from the GIT.
- To prepare the bowel before **X-ray** or colonoscopy.
- Hepatic encephalopathy (lactulose): to kill ammonia producing bacteria.
- Painful anal conditions e.g. anal fissure or piles.
- Postoperative: e.g. after hemorrhoids (piles) to avoid strain.

Contraindications of laxatives

- Laxatives are dangerous in cases of undiagnosed abdominal pain or inflammatory bowel disease. They may lead to intestinal perforation.
- Organic obstruction of the GIT.

Part 6: Therapy of Diarrhea

Causes of diarrhea

- **Infectious diarrhea:** bacterial, viral, fungal, protozoal, etc. Infectious diarrhea is the most common type.
- **Hormonal (secretory) diarrhea:** e.g. *serotonin* in carcinoid syndrome; *calcitonin* in medullary thyroid carcinoma, *histamine* in mastocytosis, *thyroxine* in hyperthyroidism. Diarrhea is caused by: (1) increased water secretions into the intestinal lumen and (2) increased intestinal motility.
- **Malabsorption syndromes:** e.g. bile acid malabsorption
- **Inflammatory (exudative) diarrhea:** caused by inflammatory bowel diseases e.g. *Crohn's disease* (transmural lesion in the small intestine) and *ulcerative colitis* (ulceration of the colon with bloody diarrhea).
- **Iatrogenic (drug induced) diarrhea:**
  - Overuse of laxatives.
  - Mg-containing antacids.

- Antibiotic-associated diarrhea (*pseudomembranous colitis*) see chemotherapy
- Cholinomimetic drugs.

Patterns of diarrhea

- **Acute self-limited diarrhea:** acute diarrhea disappears within 24 hrs.
- **Acute diarrhea (<2 weeks):** passage of watery stool more than 10 times/day associated with dehydration and electrolyte imbalance.
- **Chronic diarrhea: (>2 weeks):** persistent diarrhea for **3** weeks in adults or **4** weeks in infants. It causes weight loss and weakness.

Investigations of diarrhea

- **Stool examination:**
  - Macroscopic: consistency, color, blood, etc.
  - Microscopic: RBCs, WBCs, parasites, ova, etc.
  - Stool culture and sensitivity tests.
- **Endoscopy** and biopsy in chronic cases.
- **Radiologic** examination: by barium enema.

Treatment of diarrhea

Lines of therapy

- **Maintenance of fluid and electrolyte balance:** is the **first** priority.
- **Non-specific antidiarrheal agents:** should be applied after exclusion of other relevant causes of diarrhea.
- **Specific antidiarrheal agents:** treatment of the cause e.g.
  - Antimicrobials for infectious diarrhea.
  - Antiinflammatory drugs for inflammatory bowel diseases.
- **Antispasmodic drugs:** if there is colic or abdominal cramps.

I. MAINTENANCE OF FLUID AND ELECTROLYTE BALANCE

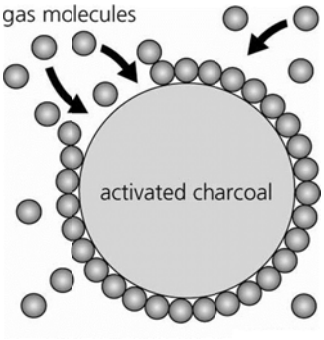
ORAL
REHYDRATION SALTS
Each sachet contains the equivalent of:
Sodium Chloride 3.5 g.
Potassium Chloride 1.5 g.
Trisodium Citrate, dihydrate 2.9 g.
Glucose Anhydrous 20.0 g.
DIRECTIONS
Dissolve in ONE LITRE of drinking water.
To be taken orally-
Infants - over a 24 hour period
Children - over an 8 to 24 hour period,
according to age or as otherwise
directed under medical supervision.
CAUTION: DO NOT BOIL SOLUTION
MANUFACTURER: Jianas Bros., Packaging Co.
Kansas City, Missouri, U.S.A.

- **Oral Rehydration Therapy (ORT):**
  - Balanced salt solution containing electrolytes and glucose (glucose is important for sodium and consequently water absorption).
  - 90% of acute cases of childhood diarrhea can be corrected using ORT only.
- **Intravenous solutions:** if dehydration is severe.

N.B. in infants with dehydration, **blood pH, serum Na^+ and K^+** must be measured before giving any **i.v. solution** to avoid electrolyte and acid/base imbalance.

II. NON-SPECIFIC ANTIDIARRHEAL THERAPY

1. Adsorbents: Kaolin, pectin, activated charcoal



Mechanism

- They adsorb water, microoganisms and toxins.
- They coat the mucosa and protect it.

Adverse effects: they may ↓ absorption of other drugs.

2. Bismuth subsalicylate

Mechanism

- Bismuth: provides a **protective coat** for the mucosa and **binds toxins** produced by pathogenic bacteria.
- Subsalicylate: hydrolyzed by intestinal bacteria into **salicylic acid** →↓ intestinal inflammation, hypermotility and secretions.

3. Anti-cholinergic drugs: atropine, hyoscine and propantheline

Mechanism

- Antidiarrheal action: ↓ colonic peristalsis by blocking the response of intestinal smooth muscle to cholinergic stimulation.
- Antispasmodic action: relieve cramps associated with diarrhea.

4. Synthetic opioid preparations: diphenoxylate and loperamide

Mechanism

- They act on opioid **μ (mu)** and **δ (delta) receptors** in the enteric nervous system (both pre- and postsynaptic) leading to:
  - ↑ segmenting (non-propulsive) contractions of the small intestine.
  - ↑ water absorption and ↓ water secretion by intestinal mucosal cells.
  - ↓ Ach release by cholinergic neurons in the ENS.
- Loperamide **cannot cross BBB** while diphenoxylate can **cross BBB in very small amount** (no CNS effects in **usual** therapeutic doses) but it can cause addiction if used in large doses and for prolonged duration.
- They are commonly **combined with atropine** (e.g. **Lomotil®** is a combination of

diphenoxylate 2.5 mg + atropine 0.25 mg) to produce more ↓↓ in intestinal motility and decrease liability for abuse.

Adverse effects

- Anti-cholinergic side effects e.g. dry mouth.
- Addiction: if used for prolonged duration.
- Precipitation of **toxic megacolon** if used in ulcerative colitis.

5. Cholestyramine

Mechanism: it binds **bile acids** in the intestine preventing their absorption and decreasing their irritation.

Therapeutic uses: diarrhea due to **bile salt malabsorption.**

III. SPECIFIC ANTI-INFECTIVE AGENTS

- It is not necessary in simple gastroenteritis as most cases are viral in origin.
- Chemotherapy is necessary in specific types of enteritis e.g.

C. difficile colitis *Clostridium difficile*	**Metronidazole** 400 mg/8h orally for 10 days (1st choice). ***If no response to metronidazole:*** **vancomycin** 250 mg/6h**.**
Campylobacter jejuni	**Azithromycin** 500 mg/day orally for 3 days.
E. coli (enterotoxigenic and enteropathogenic)	**Ciprofloxacin** 500 mg/12h for 1-3 days
Non-typhoid Salmonella spp.	**Ciprofloxacin** 500 mg/12h for 5-7 days or **ceftriaxone** 1g IV/24h.
Shigella spp.	**Ciprofloxacin** 500 mg/12h for 3-5 days or **co-trimoxazole** 2 tab (80/400)/12h.
V. cholerae	**Doxycycline** 300 mg orally single dose or **ciprofloxacin** 500 mg/12h orally for 3 days.
V. parahemolyticus	**Ciprofloxacin** 500 mg/12h for 1-3 days

IV. ANTI-INFLAMMATORY DRUGS

1. Sulfasalazine (5-aminosalicylic acid "5-ASA" + sulfapyridine)

Mechanism: In the colon, the “azo” bond is broken by intestinal bacteria to release 5-ASA and sulfapyridine: 5-ASA has anti-inflammatory and immunosuppressive, while sulfapyridine is poorly absorbed sulfonamide with antibacterial action.

Therapeutic uses:

- Active ulcerative colitis (3-4 gm/day) and to maintain remission (2 gm/day).
- Rheumatoid arthritis.

Adverse effects: mainly due to sulfapyridine (sulfonamide) → drug allergy, bone marrow depression and **megaloblastic anemia** (avoided by giving **folic acid**).

Other aminosalicylates:

- **Mesalazine:** modified-release preparation.
- **Olsalazine** is a dimmer of 5-ASA. It is cleaved in the lower bowel to release 5-ASA.

2. Corticosteroids

Mechanism

- Stimulation of Na^+ absorption from the intestine.
- Anti-inflammatory action (see endocrine).

Therapeutic uses: they are given orally or as enema in severe cases.

- To control acute episodes of Inflammatory bowel diseases
- Refractory diarrhea unresponsive to other agents.

Travellers' diarrhea:

Diarrhea that occurs to travellers and tourists in high endemic areas. Transmission of infection is done through contaminated food or water.

Drug therapy:

- Prophylaxis: doxycycline (100 mg /day orally)
- Treatment: doxycycline + bismuth subsalicylate + fluids

3. Immunosuppressive agents

- **Cytotoxic drugs (azathioprine** and **6-mercaptopurine):** can be used in ulcerative colitis and Crohn's disease in small dose to avoid bone marrow depression.
- **Cyclosporine-A** use is limited for severe cases due to potential toxicity.

N.B.

- **Metronidazol** may be used in **Crohn's disease** to eradicate anaerobic bacteria.
- **Infliximab** (monoclonal antibodies): can be used in **Crohn's disease** to ↓ TNFα.
- **Aspirin** and **indomethacin** may of value in **acute diarrhea** because they ↓ PGs synthesis → ↑ absorption and ↓ secretions of intestinal fluids.
- **Clonidine** (α_2 stimulant) can be used in **diabetic diarrhea** to ↑ intestinal water absorption and ↓ electrolyte secretion.

Part 7: Drug Therapy of Gallstones (cholelithiasis)

Choleretics: are agents that increase bile production e.g. bile acids and bile salts.

Hydrocholeretics: are agents that increase volume of bile e.g. dehydrocholic acid.

Cholagogues: are agents that stimulate the evacuation of gall bladder e.g. olive oil.

The following drugs are used to dissolve non-calcified cholesterol stones:

Chenodeoxycholic acid (CDCA): It ↓ hepatic cholesterol synthesis and ↑ bile acid and phospholipid synthesis.

Ursodeoxycholic acid (UDCA)

- It is a metabolite of chemodeoxycholic acid.
- It is more potent in reduction of hepatic cholesterol synthesis without affecting the endogenous bile acid synthesis.
- Both CDCA and UDCA are given orally in a dose of 10-15 mg/kg/day for 6-12 month.
- Diarrhea is common side effect with CDCA but is unusual with UDCA.

Notes

Clinical
Pharmacology
Department

Mansoura Faculty of Medicine

Review Questions

1. Classify laxatives. Mention the mechanism of action of each class.
2. Mention the mechanism of action and adverse effects of each of the following:
   - Metoclopramide.
   - Cimetidine
   - Omeprazole
   - Senna
   - Lomotil
3. Mention the mechanism of action and therapeutic uses of:
   - Papaverine
   - Sulfasalazine
   - Terlipressin
4. Mention the drug-drug interactions of metoclopramide.
5. Mention 2 drugs used for the treatment of nausea and vomiting due to the following conditions. For each drug, mention the mechanism of action and the main adverse effects:
   - Vomiting due to cancer chemotherapy
   - Motion sickness
6. Give the reason for:
   - Atropine is combined with diphenoxylate in Lomotil preparation.
   - Domperidone, and not metoclopramide, is used for treatment of vomiting due to levodopa.
   - Irritant laxatives should not be given for long period.
   - Folic acid should be supplemented with sulfasalazine during treatment of ulcerative colitis and rheumatoid arthritis.
7. Mention 3 differences between:
   - Metoclopramide and domperidone.
   - Cimetidine and omeprazole.
8. Mention the mechanism and management of portosystemic encephalopathy.
9. Mention the essential lines of the treatment of bleeding esophageal varices.

Of each of the following questions, select ONE BEST answer:

1. Toxicities of cimetidine include which one of the following?
A. Blurred vision
B. Diarrhea
C. Orthostatic hypotension
D. P450 inhibition
E. Sleepiness

2. Which of the following will result from blockade of H2 receptors?
A. Decreased cAMP in cardiac muscle
B. Increased cAMP in cardiac muscle
C. Decreased IP3 in gastric mucosa
D. Increased IP3 in gastric mucosa
E. Increased IP3 in smooth muscle

3. Which of the following is most effective in the treatment of peptic ulcer disease?
A. Cimetidine
B. Lanzoprazole
C. Pirenzepine
D. Ondansetron
E. LSD

4. A 55-year-old woman with insulin dependent diabetes of 40 years' duration complains of severe bloating and abdominal distress, especially after meals. Evaluation is consistent with diabetic gastroparesis. The drug you would be most likely to recommend is:
A. Docusate
B. Dopamine
C. Loperamide
D. Metoclopramide
E. Sucralfate

5. The steatorrhea of pancreatic insufficiency can best be treated by:
A. Cimetidine
B. Misoprostol.
C. Bile salts.
D. Pancreatic lipase.
E. Secretin

6. A drug of choice in the therapy of inflammatory bowel disease is:
A. Sulfadiazine.
B. Sulfasalazine.
C. Sulfapyridine.
D. Sulfamethoxazole.
E. Salicylate sodium

7. An important drug in the therapy of portal systemic encephalopathy is:
A. Lactulose.
B. Lactate.
C. Loperamide.
D. Lorazepam.
E. Doxapine.

8. Bismuth salts are thought to be effective in peptic ulcer disease because they have bactericidal properties against:
A. Escherichia coli.
B. Bacteroides fragilis.
C. Clostridium difficile.
D. Helicobacter pylori.
E. Staphylococcus aureus.

9. Misoprostol has a cytoprotective action on the gastrointestinal mucosa because it:
A. Enhances secretion of mucus and bicarbonate ion.
B. Neutralizes acid secretion.
C. Antagonizes nonsteroidal anti-inflammatory drugs (NSAIDs)
D. Relieves ulcer symptoms.
E. Coats the mucosa.

10. The primary pharmacologic action of omeprazole is the reduction of:
A. Volume of gastric juice.
B. Gastric motility.
C. Secretion of pepsin.
D. Secretion of gastric acid.
E. Secretion of intrinsic factor.

11. Cimetidine slows the metabolism of many drugs because it inhibits the activity of:
A. Monoamine oxidase (MAO)
B. Tyrosine kinase.
C. Hydrogen - potassium - adenosine triphosphatase (H+, K+, ATPase).
D. Phase II glucuronidation reactions
E. Cytochrome P450.

12. The absorption of iron is reduced when large and prolonged doses of which of the following drugs are given?
A. Vitamin C
B. Alum hydroxide.
C. Aspirin.
D. Cimetidine.
E. Lactuolse.

13. Omeprazole, an agent for the promotion of healing of peptic ulcers, has a mechanism of action that is based on:
A. Prostaglandins.
B. Gastric secretion.
C. Pepsin secretion.
D. H+, K+, ATPase.
E. Anticholinergic.

14. An effective antidiarrheal agent that inhibits peristaltic movement is:
A. Clonidine.
B. Bismuth subsalicylate.
C. Oral electrolyte Solution.
D. Pectin.
E. Diphenoxylate.

15. The approved indication for misoprostol:
A. Reflux esophagitis.
B. Regional ileitis.
C. Ulcerative colitis.
D. Prevention of gastric ulceration in patients using large doses of aspirin like drugs.
E. Pathologic hypersecretory conditions such as Zolinger- Ellison syndrome.

16. Metoclopramide has antiemetic properties because it:
A. Lowers esophageal sphincter pressure.
B. Is a central dopamine- receptor antagonist.
C. Is a central opioid receptor agonist
D. Has cholinomimetic properties.
E. Has sedative properties.

17. Fomatidine has the following properties:
A. A potent proton pump inhibitor.
B. A potent antiemetic agent.
C. A potent inhibitory effect on cyt P450.
D. A potent anti-anderogenic action.
E. None of the above.

18. Radiation-induced vomiting can be treated by drugs that act on:
A. 5-HT3 receptors.
B. M1 receptors.
C. H1 receptors.
D. Alpha receptors
E. Beta receptors.

19. Cholesterol gallstones may be dissolved by oral treatment with:
A. Lovastatin.
B. Dehydrocholic acid.
C. Methyl teriary butyl ether.
D. Chenodeoxycholic acid.
E. Monoctanoin.

20. A patient who must take verapamil for hypertension and angina has become constipated. Which of the following drugs would be most suitable as a long term laxative?
A. Aluminum hydroxide
B. Diphenoxylate
C. lactulose
D. Metoclopramide
E. Mineral oil

21. Your cousin is planning a three-week trip overseas and asks your advice regarding medications for traveler's diarrhea. A drug suitable for non-infectious diarrhea is
A. Aluminum hydroxide
B. Bismuth subcitrate
C. Magnesium hydroxide
D. Metoclopramide
E. Mineral oil

22. Which of the following drugs or drug groups is not useful in the prevention of nausea and vomiting induced by cancer chemotherapy:
A. Dexamethasone
B. Dronabinol
C. Scopolamine
D. Ondansetron
E. Metoclopramide

23. A patient presents with Zollinger-Ellison syndrome due to a gastrinoma. He has two bleeding ulcers and diarrhea. A drug that irreversibly inhibits the H+/K + ATPase in gastric parietal cells is
A. Cimetidine
B. Cisapride
C. Glycopyrolate
D. Omeprazole
E. Ondansetron

24. A drug that is recently linked with some cases of cardiac arrhythmias and sudden death is:
A. Aluminum hydroxide
B. Lactulose
C. Loperamide
D. Ranitidine
E. Domperidone

25. One recognized advantage of domperidone over metoclopramide as a prokinetic agent is:
A. More prominent antiemetic action
B. More powerful stimulant of GIT motility
C. Less CNS adverse effects.
D. Less incidence of diarrhea
E. Less cardiac adverse effects

26. A cannabinoid receptors agonist that is useful for prevention of nausea and vomiting due to cancer chemotherapy is:
A. Dronabilone
B. Morphine
C. Diphenoxylate
D. Naloxone
E. Ondansetron

27. A pregnant woman with 28 weeks gestation complaining of distressing constipation. Which of the following drugs can be prescribed safely?
A. Ondansteron
B. Lactulose
C. Senna
D. Magnesium sulphate salt
E. Castor oil

28. Bisacodyl frequently can cause:
A. Abdominal cramps
B. Constipation
C. Skin rashes
D. Dizziness
E. Nauseas

29. Patients with acute bleeding due to ruptured esophageal varices could be managed by:
A. i.v. terlipressin
B. i.v. sodium bicarbonate
C. Oral lanzoprazole
D. i.v. hydrocortisone
E. Oral lactulose

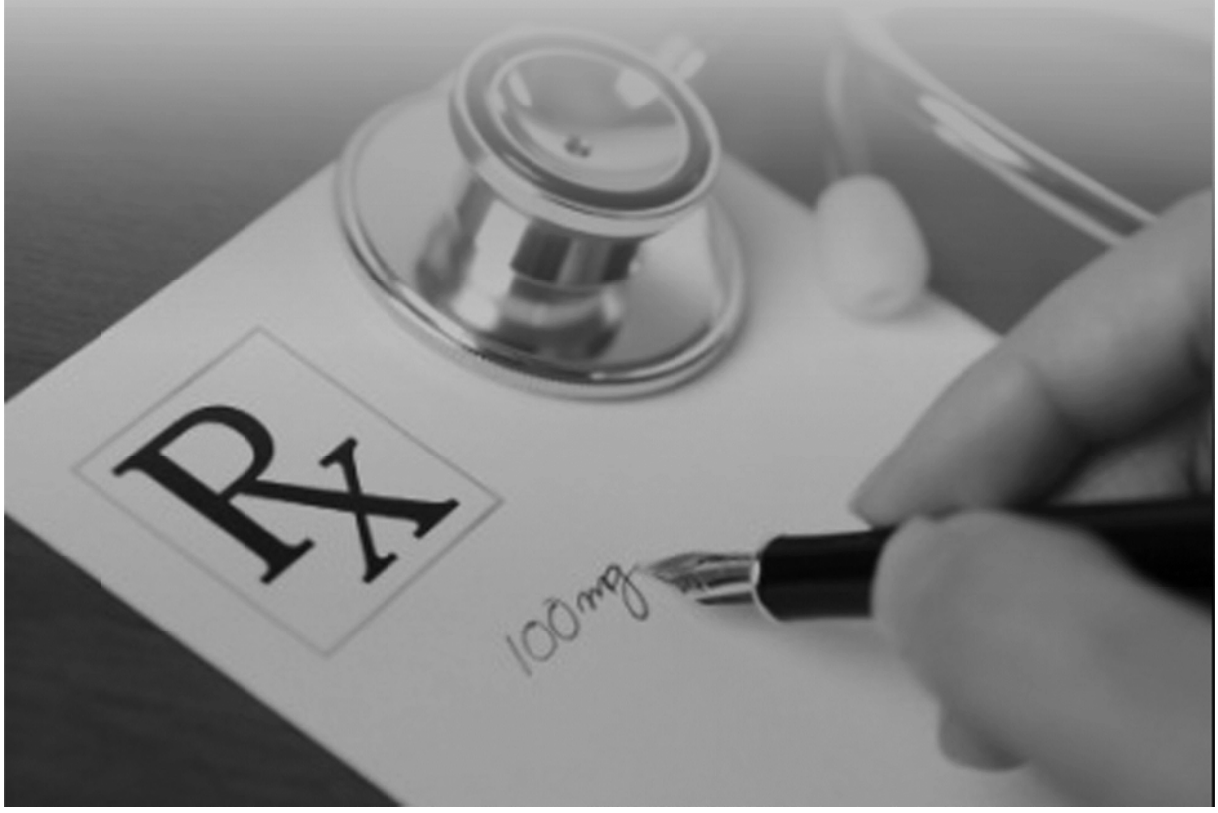
30. A patient being cared for by the gastroenterology service is being treated with sulfasalazine. Which of the following is the most likely purpose for which it is being given?
A. Antibiotic-associated pseudomembranous colitis
B. E. coli–induced diarrhea
C. Gastric H. pylori infections
D. Inflammatory bowel disease
E. NSAID-induced gastric ulcer prophylaxis

Answers

1 D	7 A	13 D	19 D	25 C
2 A	8 D	14 E	20 C	26 A
3 B	9 A	15 D	21 B	27 B
4 D	10 D	16 B	22 C	28 C
5 D	11 E	17 E	23 D	29 A
6 B	12 B	18 A	24 E	30 D

Chapter 9

Endocrine Pharmacology



Chapter 9
Endocrine Pharmacology

Part 1: Diabetes Mellitus and Antidiabetic Drugs

Definition of DM: It is a clinical syndrome characterized by disturbance in carbohydrates, fat, & proteins metabolism due to either *insulin deficiency* or *insulin resistance*.

Manifestations:

- Polyuria, polydipsia, polyphagia, and loss of weight.
- Complications of DM e.g. recurrent infections, angiopathy, retinopathy, nephropathy, DKA, etc.

Histology

There are **4** types of cells in the islets of Langerhans.

- **α cells** (20%) : secrete **glucagon**.
- **β cells** (75%) : secrete **insulin** and islet associated polypeptide (amylin).
- **δ cells** (3-5%) : secrete **somatostatin**.
- **F cells** < 2 %: secrete **pancreatic polypeptides** (facilitate digestive process).

Laboratory investigations:

- Urine analysis for glucosuria & ketonuria.
- Blood glucose: fasting and 2-hr after oral 75 g glucose.
- Glycated hemoglobin (HbA_1C): indicates average blood sugar level for the past 2-3 months

	Normal	IGT*	DM
Fasting BG	< 100 mg/dl	100-126	**> 126** mg/dl
2 hr after oral 75 g glucose	< 140 mg/dl	140-200	**> 200** mg/dl
HbA_1C	< 6%	6-6.5%	**> 6.5%** Elevated levels mean uncontrolled DM over the last **2-3** months.

*** IGT = Impaired glucose tolerance (prediabetes):** it can be controlled by **diet regime** alone.

Common types of DM:

- **Type 1 DM:** (old name: insulin dependent DM)
- **Type 2 DM:** (old name: non-insulin dependent DM)
- **Gestational DM:** appears during pregnancy and disappears after labor.

	Type 1 (IDDM)	Type 2 (NIDDM)
Pathophysiology:	Autoimmune condition against the pancreatic beta cells. The damaged pancreas **doesn't make** insulin.	The pancreas usually produces some insulin. But either the amount is **not sufficient**, or the body's cells are **resistant** to it.
Onset (age):	< 30 years	>30 years (adult-onset)
Body built:	Usually undernourished	Usually obese
Insulin therapy:	Essentially required.	Required in 20% of patients
Oral drugs:	Not required.	Essentially required.

Less common types of DM:

- **Latent autoimmune diabetes of adults (LADA):** is a condition in which type 1 DM develops in adults.
- **Maturity onset diabetes of the young (MODY):** is a condition in which type 2 DM develops in children or young adults who develop persistent, asymptomatic hyperglycemia without progression to diabetic ketoacidosis.

> **N.B.** *Adults with LADA or children with MODY are frequently misdiagnosed as having type 2 or type 1 DM, based on age rather than etiology.*

- **Secondary DM:** 2ry to drugs, infections, endocrine diseases, etc.

Lines of treatment:

- **Diet control**.
- **Diet + insulin (type 1).**
- **Diet + oral antidiabetic drugs (type 2).**
- **Exercise**: to enhance peripheral glucose utilization.

DIET REGIME

It is the **first line** of treatment in all types of DM.

✸ Glycemic Index (GI):

– It describes the capacity of a food to raise blood glucose in normal glucose

tolerant individuals.

– Foods with a high GI may be associated with ↑ risk of obesity and the postprandial hyperglycaemia, with such foods may also ↑ the risk of T2DM.

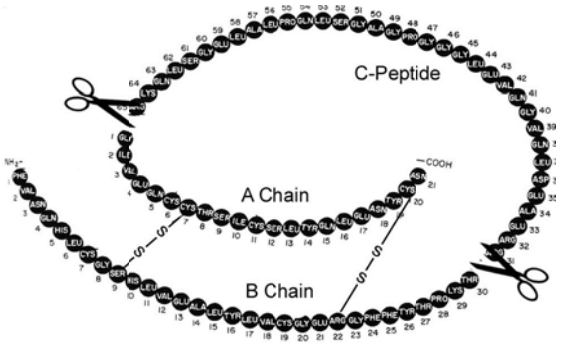
Caloric requirements of patients	
Average wt:	**30**-35 c/kg/d
Children or thin:	**40**-45 c/kg/d
Obese:	**20**-25 c/kg/d

Distribution of food elements
15 % from proteins
55 % from carbohydrates
30 % from fats

INSULIN

Chemistry

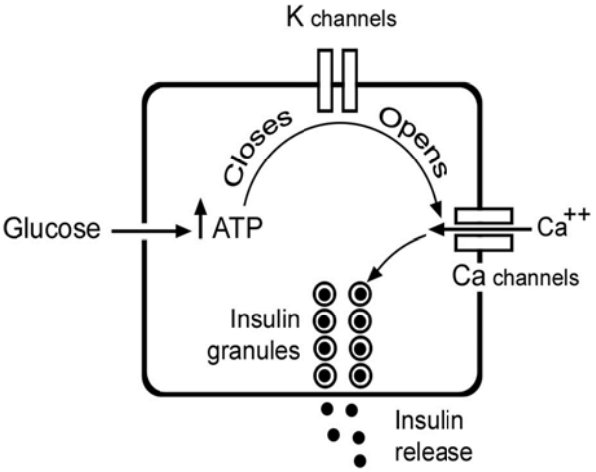
- 2 peptide chains: A (21 aa) and B (30 aa) linked by 2 disulfide bonds.
- Insulin is secreted as **proinsulin** then cleaved (within the storage granules in the β cells) into insulin and connecting peptide "C-peptide".



N.B. Measurable C-peptide levels indicate the presence of endogenously produced insulin and functioning β-cells.

Secretion

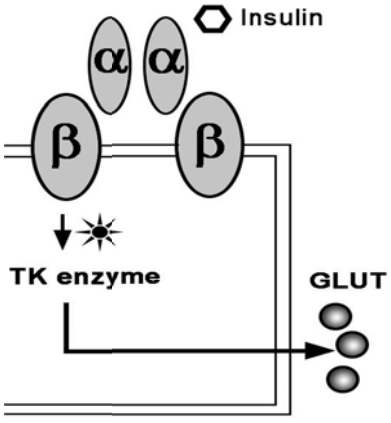
- Glucose enters β cells → ↑ ATP → closure of ATP-dependent K^+ channels → opening of voltage-gated Ca^{2+} channels → ↑ Ca^{2+} influx → insulin release.



Insulin receptors

– **A tyrosine kinase receptor** consists of 2 extracellular **α**-subunits and 2 transmembrane **β**-subunits.

– Binding of insulin to the α-subunits causes activation of the β-subunits → activation of **tyrosine kinase enzyme** which triggers a series of intracellular effects that ↑ number of **glucose transporters** (especially **GLUT4**) on the cell membrane → ↑ transport of glucose into the cell.



Up-regulation of insulin receptors:	Down-regulation of insulin receptors:
▪ **Insulin deficiency** (e.g. in fasting) ▪ **Drugs: INSULIN SENSITIZERS:** a) Thiazolidinediones: e.g. pioglitazone & rosiglitazone. b) Trace elements: e.g. selenium & chromium.	▪ **Insulin excess (Obesity)**. Obesity causes continuous stimulation of β-cells → hyperinsulinemia → down regulation of insulin receptors. ▪ **Drugs: e.g. corticosteroids**

Pharmacokinetics of insulin

- **Endogenous insulin:**
  - The pancreas releases insulin in the portal vein in small bouts at short intervals according to blood glucose levels. The liver clears ~ 50% of the secreted amount; the rest is distributed all over the body and cleared by receptor-mediated uptake and intracellular degradation.
  - The normal blood level of insulin is **5-15 μU/ml** (fasting) and **60-90 μU/ml** (postprandial).
- **Exogenous insulin:**
  - Insulin is not administered orally because it is rapidly destroyed by GIT enzymes. It is given **s.c.** (common) or **i.v.** (in emergencies).
  - The plasma **half-life** of insulin given **intravenous** is **10-12 min**.

Sources of commercial insulin

- **Traditional (animal) insulin:**

- Prepared from animals (beef and pork).
- P**O**rk insulin differs from human insulin in **O**ne aa (*alanine* in pork and *threonine* in human) while b**EE**f insulin differs from human in thr**EE** aa.
- Animal insulin may contain traces of animal proteins and proinsulin, so it is **more antigenic** and can cause insulin resistance.

- **Human insulin:**

- It is identical to human insulin and is prepared by recombinant DNA technology (genetic engineering) from yeasts or bacteria.
- Advantages: **Less antigenic** and rare development of insulin resistance.

- **Insulin analogs:**

- Recombinant insulin analogs are now available in which some amino acids in the "normal" insulin have been switched (e.g. insulin lispro) or replaced (e.g. insulin glargine), making a “different molecule” so as to get different pharmacokinetic properties.

Common examples of insulin preparations

Category	Generic name/Brand	Features	Onset	Peak	Duration
RAPID ACTING ANALOGS	**Insulin glulisine** **Insulin lispro** **Insulin aspart**	– They are human insulins that have been modified at 1–2 amino acids in the B chain to increase their solubility. – They are the fastest acting insulins. They must be injected just before meals.	5-15 min	1-2 h	3-5 h
SHORT ACTING INSULIN	**Regular; soluble; neutral** (Humulin R; Novolin R)	– It is identical to human insulin – It is the only type that can be given **i.v.** in diabetic emergencies e.g. diabetic ketoacidosis.	30 min	2-4 h	6-8 h
INTERMEDIATE ACTING	**NPH (isophane)*** (Humulin N; Novolin N)	– It is made by addition of the protein **P**rotamine to **N**eutral insulin to prolong its duration.	1-2 h	4-6 h	12-16 h
LONG ACTING INSULIN	**Insulin glargine** (Lantus) **Insulin detemir** **Insulin zinc suspension**	– They are insulin analogs with minor amino acid changes to make them long acting "peakless". – It is human insulin added to ↑↑ amount of zinc – They are usually administered once daily.	1-2 h	None	18-24 h
PREMIXED INSULIN (Biphasic)	**Humulin 70/30; Mixtard** (70% NPH – 30% regular) **Humalog Mix 75/25** (75% NPH – 25% lispro)	– They provide rapid onset and relatively prolonged duration – They are usually injected twice daily.	< 30 min		12-16 h

- NPH = Neutral Protamine Hagedorn
- Regular insulin can be mixed with NPH in the same syringe. The mixing order should be the clear regular drawn up *first* then the cloudy NPH (i.e. "clear-to-cloudy").
- NPH, insulin zinc and biphasic insulin are **cloudy** in appearance.

Insulin administration

- All insulins are given by **s.c. injection.**
- **Regular insulin** is the only type that can be given **i.v.** in **diabetic emergencies**.
- The standard insulin concentration is 100 units/mL (U-100). It should be injected with a standard U-100 syringe.

Insulin requirement and long term regimens

- Generally, the total daily insulin requirement in units is equal to 0.55 times the person's weight in kilograms. A conservative total daily dose (TDD) of 0.4 units/kg/d is given initially to a newly diagnosed patient; the dose is then adjusted according to the blood glucose level.

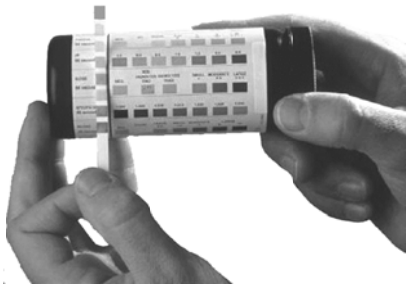
- **Basal-bolus regimen:**
  - Give **long acting insulin** at bed time; plus three daily injection of **short acting insulin** before each meal. The long-acting insulin provides basal level of insulin that controls blood glucose during night and in-between meals, and the short acting insulin controls postprandial hyperglycemia.
  - It is commonly used for patients with Type-1 DM and in pregnant women with diabetes.

- **Twice-daily biphasic insulin regimen:**
  - Use biphasic insulin. The average daily requirement is 0.5 units/kg. Use the two-thirds rule:
  - Give the 2/3 of the TDD in the morning and the 1/3 at evening.
  - It is commonly used for patients with Type-2 DM

- **Insulin pump** (artificial pancreas): insulin is automatically released according to continuous measurement of blood glucose by electronic sensor.

Methods of administration

- S.c. injection (using insulin syringes).
- Portable pen injector (Novo® pen).



Follow up of insulin therapy

By estimation of glucose in **urine** using urine dipsticks or from **capillary** blood glucose level using portable glucometers.

Indications of insulin

- Type 1 DM.
- Type 2 DM in some conditions:
  - *After failure of oral drugs.*
  - *If the patient of type 2 got **"stress conditions"** e.g. infections, surgery, or pregnancy.*
- Diabetic ketoacidosis: **regular insulin** is the only type used **i.v.**
- Hyperkalemia (insulin + glucose i.v.): insulin ↑ shift of K^+ from blood to tissues.

Adverse effects of insulin

- **Hypoglycemia:** the most common and dangerous side effect.
- **Hypokalemia:** insulin causes shift of K^+ from extra- to intracellular fluid.
- **Hypersensitivity reactions:** urticaria, angioedema or anaphylactic shock.
- **Insulin resistance** (see below).
- **Local adverse effects:**
  - **Allergy:** at the site of injection, especially with animal insulin.
    Treatment:
    - Change the type of insulin.
    - Local corticosteroids.
  - **Lipodystrophy: (atrophy** or **hypertrophy)** of s.c. tissue after repeated injections.
    Treatment: rotating the injection site.
  - **Local infection**.

Insulin resistance (IR)

Definition: failure of the body cells to respond to either endogenous or exogenous insulin. As a result, larger doses of insulin are required to give the desired response.

Causes and mechanism of IR:

- Pre-receptors defect (Immunological): due to formation of antibodies against insulin.
- Receptor defect: due to **down-regulation** of insulin receptors e.g. in:
  - The metabolic syndrome: it is a combination of *central **obesity***, *hypercholesterolemia*, *heart disease, type2 DM* and *IR*.
  - Pregnancy.
  - Severe infection or stress.
  - Drugs: e.g. corticosteroids.

- Post-receptor defect (intracellular): abnormal signal transduction due to **genetic** defect.
- Local insulin resistance: due to degradation of insulin in s.c. tissue by proteolytic enzymes. It is **diagnosed by** changing the route of administration to i.v. injection. If there is good response, then the resistance is local.

Treatment of IR:

- **Life-style modification:**
  - Strict diet control.
  - Weight reduction.
  - Physical exercise.
- Correction of any **precipitating factor:** e.g. **infection** or **stress**.
- **Metformin:** to improve receptor sensitivity and ↓ intestinal glucose absorption (see later).
- **Thiazolidindiones (Insulin sensitizers):** e.g. pioglitazone to ↑ insulin sensitivity (see later).
- Change the site of injection regularly In cases of **local** insulin resistance

Hepatitis C makes people three to four times more likely to develop type 2 DM and insulin resistance.

ORAL ANTIDIABETIC DRUGS

1. Sulfonylureas

- Sulfonylureas are the most widely used medications for the treatment of T2DM.
- All of the sulfonylureas are well absorbed after oral administration and bind to plasma proteins.

Classification

- **First-generation compounds: chlorpropamide, tolbutamide, acetohexamide.**
- **Second-generation compounds: glibenclamide, glyclazide** and **glipizide**; they are up to 200 times more potent than first-generation agents.
- **Third-generation compounds:** e.g. **glimepiride**; these compounds may interact with different cellular proteins than other sulfonylureas.

Mechanism of action

- **Pancreatic action:**
  - Sulfonylureas ↑ **insulin secretion** by pancreatic β cells. They block K^+ channels in β cells, leading to depolarization, increased Ca^{2+} entry via voltage-dependent calcium channels, and increased insulin secretion.
  - They ↓ **serum glucagon**, which opposes the action of insulin.

- **Extrapancreatic action:**
  - They ↑ **insulin receptor sensitivity**, may be by increasing the number of insulin receptors. However, sulfonylureas do not decrease the insulin requirements of patients with type I diabetes.
  - They ↓ **hepatic output of glucose** (gluconeogenesis).

Therapeutic uses

- Type 2 DM (they are not effective in type 1 DM).
- **Chloropropamide** may be used in treatment of nephrogenic diabetes insipidus (it ↑ sensitivity of renal tubules to ADH).

Adverse effects

- **Hypoglycemia** especially with long acting drugs (chlorpropamide) or in elderly patients with hepatic or renal dysfunction .. *(contraindicated in renal failure).*
- Increased appetite and **weight gain.**
- **Pharmacologic failure** is common, initially affecting 15%–30% of patients (1ry failure) and 90% after 6–7 years of therapy (2ry failure). It is due to progressive decline in β cell function.
- **Hepatotoxicity** (cholestatic hepatitis) .. *(contraindicated in liver disease)*.
- **Allergic reactions**.

2. Meglitinides: repaglinide and nateglinide

- They **increase insulin secretion** by the same mechanism like sulfonylureas although the binding site on the β-cells is different.
- They have very **fast onset** and **short duration** so; they are taken **orally** just *before meals* to control **postprandial hyperglycemia**.
- They **don't contain sulfur**, so they can be used in patients allergic to sulfonylureas.
- **Hypoglycemia** is the major side effect.
- They should be used with caution in patients with **hepatic or renal impairment**.

3. Biguanides: metformin

Mechanism of action

- ↓ **intestinal glucose absorption** and ↓ hepatic gluconeogenesis. It does **not** increase insulin secretion (so it doesn't cause hypoglycemia).
- ↑ insulin receptors sensitivity.

Therapeutic uses

- Type 2 DM either alone (in mild cases) or in combination with other drugs.
- To enhance weight loss in **obese patients** (↓ glucose absorption).
- Recent studies showed that metformin is useful in the treatment of **polycystic ovary syndrome (POS)**; it lowers serum androgen levels and restores normal menstrual cycles and ovulation.

Adverse effects

- GIT upset (the most common): anorexia, vomiting, and diarrhea.
- ↓ absorption of vitamin B_{12}: rarely a clinical problem.
- Lactic acidosis: due to increased **anaerobic glycolysis** especially in patients with severe **renal** or **hepatic** diseases or if taken with **alcohol**.

4. Thiazolidinediones (insulin sensitizers): Pioglitazone – Rosiglitazone*

Mechanism of action

- They act on **nuclear genes** called peroxisome proliferator-activated receptor-gamma (PPAR- γ) present in muscles, adipose tissue, and liver cells **leading to:**
  - They ↑ insulin receptor **sensitivity** (by about 60%) and ↓ insulin resistance.
  - They ↑ number of glucose **transporters** →↑ glucose uptake.
  - They have beneficial effect on serum **lipoprotein** levels (↓TGs).
- They have **slow onset** and **prolonged duration** because their mechanism involves gene regulation.

Therapeutic uses: To improve **insulin resistance in type 2 DM.**

Adverse effects

- Hepatotoxicity
- Fluid retention leading to peripheral edema & **weight gain**. (They should be avoided in patients with CHF).

***N.B** pioglitazone is now the only thiazolidinedione on the market.

5. α-Glucosidase inhibitors (starch blockers): Acarbose – Miglitol

- They act by **competitive inhibition of intestinal *α-glucosidase enzyme*** → ↓ digestion & absorption of carbohydrates.
- **GIT side effects** are common: flatulence, diarrhea, abdominal pain.
- They should be avoided in patients with **inflammatory bowel disease.**

NEWER ANTIDIABETIC DRUGS

Incretins are group of metabolic peptides released by gastric and intestinal cells after eating to stimulate insulin secretion and lower plasma glucose. They are rapidly inactivated by the enzyme **dipeptidyl peptidase 4 (DPP-4).** The most important incretin peptide is **glucagon-like peptide-1 (GLP-1).**

1. Incretin (GLP-1) mimetics: Exenatide

Exenatide is a synthetic 39-amino acid GLP-1 analog; **liraglutide** is longer acting analog and more resistant to metabolism.

Mechanism of action

- They ↑ insulin secretion and ↓ glucagon secretion.
- They slow gastric emptying and ↓ appetite.

Therapeutic uses

- Type 2 DM either alone or in combination with **oral drugs**. (It should not be given with insulin).
- They are given **parenterally** (**s.c.**) 60 min **before** breakfast and dinner. (It should not be given **after** a meal).

Major adverse effects: nausea, vomiting, and **pancreatitis** (may be serious).

2. Dipeptidyl peptidase 4 inhibitors (Gliptins): Sitagliptin - Saxagliptin

Mechanism of action

- They **inhibit dipeptidyl peptidase 4 (DPP-4)**, the enzyme responsible for the proteolysis of the incretin GLP-1.
- DPP-4 inhibitors may also **improve β-cell function**.

Therapeutic uses

- Type 2 DM either alone or in combination with **metformin**.
- They are given **orally**; most common **side effects** are headache and nausea.

3. Amylin analogs: Pramlinitide

- **Pramlintide** is a synthetic amylin analog. Amylin is a polypeptide secreted by β-cells of the pancreas, and it acts in concert with insulin to reduce blood sugar.
- It is **injected s.c.,** typically with insulin.
- Common side effects are hypoglycemia and nausea.

Drug interactions with oral hypoglycemic drugs

Drugs potentiate the hypoglycemic effect:	Drugs antagonize the hypoglycemic effect:
▪ Microsomal enzyme inhibitors. ▪ **β-blockers:** ↓ hepatic glycogenolysis ▪ **Salicylates:** displacement of sulfonylureas from plasma proteins.	▪ Microsomal enzyme inducers. ▪ **β-agonists:** ↑ hepatic glycogenolysis. ▪ **Thiazides** and **diazoxide:** they open ATP sensitive K+ channels → ↓ insulin release and ↓ peripheral glucose utilization. ▪ Anti-insulin hormones: e.g. steroids and glucagon.

TREATMENT OF DIABETIC COMPLICATIONS

Hypoglycemic coma

Causes:
- Large dose of insulin or sulfonylurea.
- Missed meal while taking insulin or sulfonylureas.
- Vigorous muscular exercise without dietary adjustment.

Manifestations:
- Sympathetic overactivity: tremors, cold sweating, mydriasis, tachycardia, etc.
- Hunger pain, mental confusion, and coma.

Treatment:
- If the patient is conscious or semiconscious → give oral sugar solution.
- If the patient is in deep coma: (1) i.v. glucose 10%; (2) Glucagon 1 mg i.m.

Hyperglycemic coma (diabetic ketoacidosis; DKA):

Causes:
- Excess food intake.
- Inadequate insulin administration.
- Infection or stress condition.

Manifestations (DKA):
- **D**ehydration and dry shrunken tongue.
- **K**etosis: smell of acetone in breath and ketones in urine.
- **A**cidosis (pH < 7.3) → acidotic breathing (rapid and deep).
- Deep coma in late cases.

Treatment:

- **Fluid replacement:** fluid deficit = 4-5L.
  - Use normal (0.9%) saline. Ringer's lactate is also acceptable choice.
  - Start with 1–2 L/h for the first 2 hours, followed by 500 mL/h for 6 hours.
  - Potassium: is routinely added to the i.v. fluid as 20 mEq KCl/1L.
- **Regular insulin:**
  - Start with a bolus of dose of 0.1 units/kg i.v. followed by an infusion of 0.1 units/kg/hour.
  - Insulin infusion should continue until serum electrolytes, pH, and glucose level are normalized.
  - Glucose 5 % is given when blood glucose falls to ~250 mg/dl *to prevent cerebral edema.*
- **Bicarbonate (HCO_3):** is not routinely given unless there is severe acidosis (pH < 7.1).

Hyperosmolar hyperglycemic state (HHS):

- HHS was previously termed *hyperosmolar hyperglycemic nonketotic coma* (HHNC); however, the terminology was changed because coma is found in fewer than 20% of patients with HHS.
- It is a life-threatening medical emergency that is more common in old age.
- Pathogenesis: severe hyperglycemia causes ↑ water loss (osmotic diuresis) with little sodium loss → severe dehydration with hyperosmolarity. **Ketoacidosis is absent.**

	DKA	HHS
BG	> 250 mg/l	> 600 mg/l
pH	< 7.3	> 7.3
Ketonuria	++	--

Treatment: similar to DKA **except in**:

- **Fluid replacement:** fluid deficit >5L.
  - Rapid and aggressive i.v. isotonic saline is the principal treatment. The patient may require 5-8 L of saline.
  - Fluid replacement alone can reduce glucose levels.
- **Insulin** i.v.i similar to DKA. *Insulin used without concomitant vigorous fluid replacement increases the risk of shock.*
- Hypokalemia is usually less marked but **potassium** may be required early in the treatment.
- **LMWH** to prevent thrombotic complications.

Diabetic neuropathy

Diabetic neuropathy is the most common complication of diabetes mellitus (DM), affecting as many as 50% of patients with type 1 and type 2 DM. It may be cranial, sensory, sensory-motor or autonomic. DN is an irreversible process.

Pathogenesis

- **Advanced glycated end-products:** elevated intracellular levels of glucose cause a non-enzymatic covalent bonding with cellular proteins, causing microvascular damage, ischemia, hypoxia, and nerve damage.
- **Polyol pathway (sorbitol/aldose reductase pathway):** elevated intracellular glucose is converted into sorbitol via the enzyme *aldose reductase*. Sorbitol is toxic to tissues.

Treatment

- Tight, stable glycemic control is the most important factor for slowing progression of DN.
- **For neuropathic pain**, and tingling sensation: duloxetine (antidepressant drug) 30 mg/12h orally (first choice) or pregabalin (second choice).
- **For diabetic gastroparesis:** metoclopramide
- **For erectile dysfunction:** sildenafil

Part 2: Medical Treatment of Obesity

Basic information

Leptin

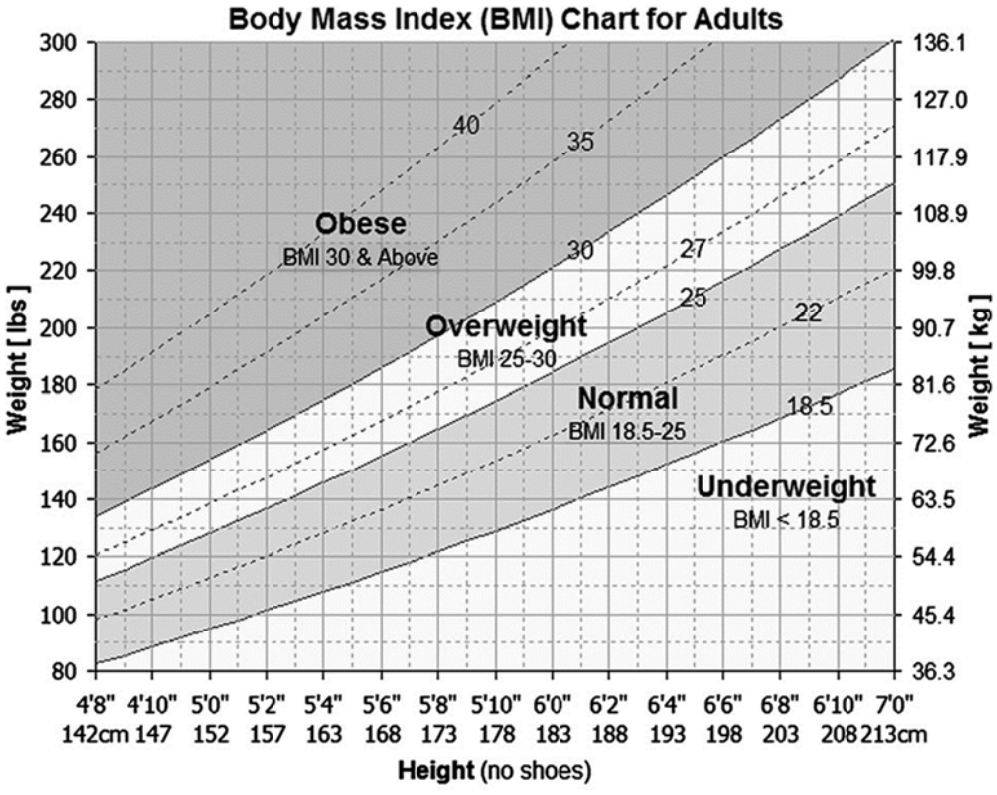
- It is thought to play a key role in the regulation of body weight.
- It is **produced (synthesized)** by **adipose tissue** and **acts on** satiety centers in the hypothalamus to ↓ appetite (i.e. **Leptin induces satiety**).
- As such when patients reach a certain peripheral fat mass, leptin acts as a **lipostat** to **reduce food intake**.

Ghrelin

- **Ghrelin stimulates hunger**.
- It is produced mainly by the fundus of the **stomach** and pancreas.
- Ghrelin levels ↑ before meals and ↓ after meals.

The body-mass index (BMI) – (Kg/m2)

- Normal: 18-25
- Overweight: 25-30
- Obese: >30
- Morbid obesity: >40



Medical treatment

1. Orlistat (Xenical®)

- Orlistat is a **pancreatic lipase inhibitor**. It inhibits digestion and absorption of dietary fats leading to weight loss.
- Orlistat is normally used for <1 year. Patients fail to lose at least 5% of their bodyweight within 3 months, orlistat should be discontinued.
- **Adverse effects** include steatorrhea and flatulence.

2. Lorcaserin (Belviq®)

- It is recently approved selective **5-HT_{2C}** receptor **agonist** in the hypothalamus leading to weight loss through **satiety.**
- It is used for long term control of obesity.
- **Adverse effects** are mild and include mainly **headache.**

3. Liraglutide (Saxenda®)

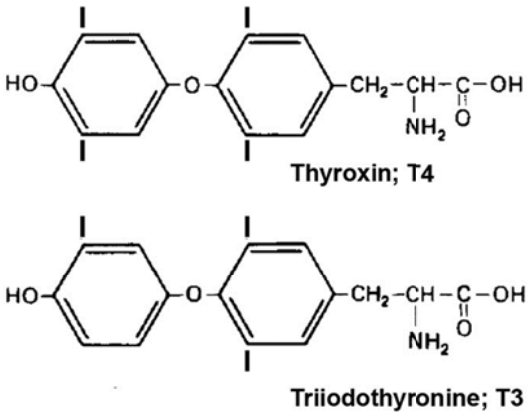
- It is an **injectable** long acting glucagon-like peptide-1 receptor agonist, binding to the same receptors as does the endogenous hormone GLP-1 that stimulates insulin secretion.
- It is developed principally for treatment of type 2 DM. In 2015, it was approved for treatment of morbid obesity in adults.

4. Sibutramine (Meridia®)

- **Centrally acting appetite suppressant** related to **amphetamine** (inhibits uptake of 5-HT and noradrenaline at hypothalamic sites that regulate food intake).
- **Adverse effects:** hypertension, arrhythmia, insomnia, and headache.
- It has been withdrawn in 2010 from the USA due to an increased risk of cardiovascular events, but still available in many countries including Egypt and Middle East.

Part 3: Thyroid Gland and Antithyroid Drugs

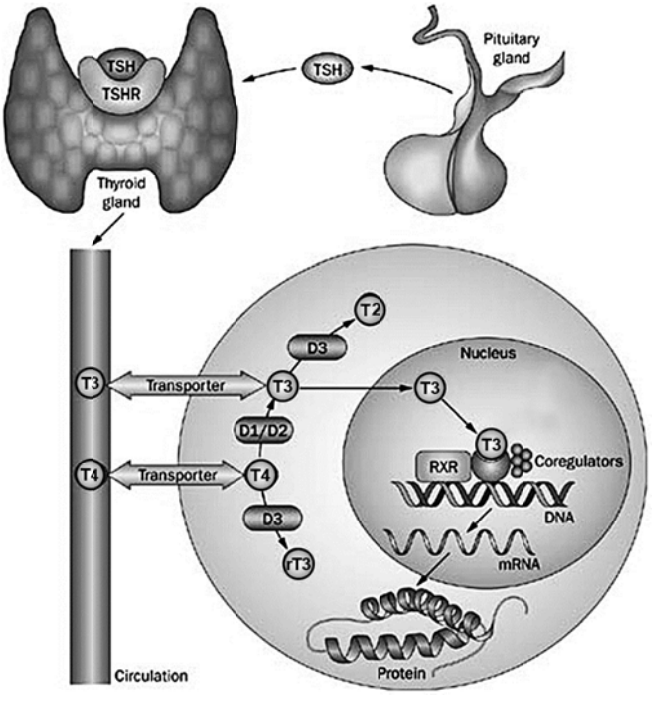
General principles



- The major hormone secreted by the thyroid is thyroxine (T_4), which is **deiodinated** in many tissues to the more potent triiodothyronine (T_3). Both are bound reversibly to thyroxine-binding globulin (TBG). Only the free (unbound) fraction enters cells and produces biological effects.
- The most important step in the process of thyroid hormone synthesis is **oxidation** (organification) of iodides by **peroxidase enzyme** to produce molecular iodine, which then attaches to tyrosine to form mono- and diiodotyrosine. T4 is formed by **coupling** of 2 diiodotyrosines, and T3 by coupling of diiodothyrosine with mono-iodotyrosine.
- T4 secretion is stimulated by thyroid-stimulating hormone (TSH). In turn, TSH secretion is inhibited by T4, forming a negative feedback loop.
- The gland synthesizes T4 > T3 (20:1) but T3 is 4-times more potent than T4.
- Most of the circulating T3 is derived from peripheral deiodination of T4.
- **B-blockers** and **corticosteroids** inhibit peripheral conversion of T4 into T3.

Preparations of thyroid hormones

- **L-thyroxine:** a synthetic sodium salt of **T4** that maintains normal T4 and T3 levels (t ½ is 7 days).
- **Liothyronine:** a synthetic sodium salt of **T3** (t ½ is 1 day).



Mechanism of action

- T3 & T4 diffuse through the cell membranes and bind to cytoplasmic receptors then transported to the **nucleus and mitochondria**, where it interacts with many **DNA receptors (genes)** and affect their function.
- Most of T3 & T4 receptors are found in pituitary, liver, kidney, heart, sk ms.
- T3 & T4 are responsible for optimal growth and development.

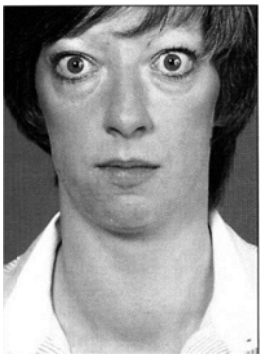
Hypothyroidism (myxedema)

- Hypothyroidism in infants leads to **cretinism** (myxedema with physical and mental retardation).
- It is treated by replacement with **L-thyroxin** (T4). The therapeutic goal is 'normalization' of the TSH level.
- Children require more T4 than adults to maintain optimal physical and mental development.
- T3 (Liothyronine) is not used for replacement therapy because L-thyroxin (T4) can maintain normal T4 and T3 levels, and also because T3 has **shorter t½** .

Hyperthyroidism (thyrotoxicosis)

Definition: It is a clinical syndrome results from high levels of thyroid hormones.

Clinical types



- **Graves' disease:**
  - It is autoimmune disease in which there are abnormal antibodies *(thyroid stimulating immunoglobulins)* activates TSH receptors in the thyroid gland.
  - The gland is diffusely enlarged and soft.
  - The treatment is usually medical.
- **Toxic multinodular goiter:** treatment is usually surgical.
- **Less common types:** e.g. subacute (de Quervain's) thyroiditis. It is due to viral infection.

The term "goiter" means any thyroid swelling which is neither inflammatory nor neoplastic. Thyroid enlargement may occur with hypo- or hyperthyroidism.

Clinical picture

- Most manifestations of hyperthyroidism resemble sympathetic overactivity because thyroxin increases sensitivity of adrenergic β-receptors to circulating catecholamines.
- There are tachycardia, arrhythmia, sweating, lid lag, exophthalmos, etc.

Investigations

- Measuring serum T3, T4, and TSH **(the most important test):** T4 is ↑ and TSH is ↓.
- Assay for positive anti-thyroid antibodies: 90% +ve in Grave's disease.
- Thyroid scan for tumors.

Management

There are **2** main lines for treatment:

- **Medical treatment:** mainly for Grave's disease.
- **Surgical thyroidectomy:** mainly for multiple nodular goiter

MEDICAL TREATMENT (ANTITHYROID DRUGS)

1. Thiouracil drugs (thioamides)
(Carbimazole – Methimazole - Propylthiouracil)

Pharmacokinetics

- Methimazole is the active metabolite of carbimazole.
- The $t_{1/2}$ of propylthiouracil is 1.5 hr while the $t_{1/2}$ of methimazole is 6 hrs.
- The short t½ of these drugs has little effect on their effect because they are selectively accumulated in the thyroid.
- Propylthiouracil is preferable during **pregnancy** because it does not cross placental barrier (because it is strongly bound to plasma protein).

Mechanism of action

- They inhibit **oxidation** of iodides into iodine by inhibiting *peroxidase enzyme.* Consequently, they inhibit **iodination** of tyrosine and **coupling** of iodotyrosine to form iodothyronines.
- Propylthiouracil also inhibits the **peripheral conversion** of T4 into T3.
- Clinical response appears after 3-4 weeks till the stored hormones are depleted from the gland (but **propylthiouracil has faster effect,** so it is used in thyrotoxic crisis).

Doses and duration

- **Carbimazole (Neomercazole):** start with 30 mg/d till reach euthyroid state (after ~4-8 weeks) then maintain on 15 mg /d for **12-18 months** *(until the gland undergo spontaneous remission).*
- **Propylthiouracil:** start with 300 mg/d for 4-8 w then 150 mg/d for **12-18 months**.

Adverse effects

- **Agranulocytosis & bone marrow depression (<1%):** it is the most dangerous side effect but it is usually reversible (see chapter Blood).
- Hypothyroidism with **increased size and vascularity** of the gland due to ↑ TSH.
- Hypothyroidism of the infant (**fetal goiter**) if given during pregnancy *(less common with PTU)*.

- **Hepatotoxicity** that may be fatal *(more with propylthiouracil)*.
- **Hypersensitivity reactions:** may require stopping of the drugs.
- There is **50-68%** incidence of **relapse**.

Precautions during thiouracil treatment

- Therapy with thiouracil drugs should continue for **1-2 years** and should be **stopped gradually** (to prevent relapse).
- Agranulocytosis is prevented by **repeated WBC count** and by observing early manifestations of the disease (sore throat & fever).
- If used during **pregnancy,** propylthiouracil is the drug of choice.

2. Radioactive iodine

Radioactive iodine is an effective **oral** treatment for thyrotoxicosis caused by **toxic multinodular goiter**. It is relatively **'safe'** and has largely replaced surgery (unless there is huge gland causing pressure symptoms).

Mechanism of action

- The isotope usually employed is **^{131}I** with a t ½ of **8** days.
- Radioactive **^{131}I** is selectively accumulated in the thyroid tissue (normal or metastatic) and emits **β rays** that destroy the gland. After 6-12 weeks of administration, the gland will shrink in size and the patient becomes euthyroid.
- **Delayed hypothyroidism** is the main adverse effect (80%); the majority of patients will require thyroxin supplementation after 5 years.

Contraindications

- **Pregnancy and lactation**: ^{131}I crosses placental barrier and excreted in milk.
- **Age < 16 years** for fear of delayed malignant changes and gonadal damage.
- **Thyroid eye disease (exophthalmos; ophthalmopathy):** radioiodine may worsen the condition.

3. β-blockers (Propranolol)

- It controls sympathetic overactivity e.g. tachycardia and arrhythmia.
- It ↓ insomnia, and tremors (blocks central and peripheral β2 receptors).
- It inhibits peripheral conversion of T4 to T3.

N.B. If propranolol is contraindicated, give **diltiazem** to control tachycardia and arrhythmia (other CCBs are less effective).

SURGICAL TREATMENT: subtotal thyroidectomy

Indications

- Failure of the medical treatment.
- Multinodular goiter with tracheal compression.
- Presence of malignancy.

Preparation of patient before operation

- **Carbimazole:** 10 mg t.d.s. 6 weeks before the operation to reach euthyroid state.
- **Potassium iodide:** 10-14 days before operation to ↓ size and vascularity of the gland (see below).
- **Propranolol:** to control HR and cardiac arrhythmia.
- **Sedatives** (diazepam): to ↓ anxiety.

Iodides

- Potassium iodides or Lugol's iodine, 5 drops twice daily is given **10-14 days** before surgery in order to:
  - Iodides inhibit synthesis and **release of T4 & T3** from the gland by inhibiting the **proteolytic enzymes** that release T4 & T3 from thyroglobulin (the main mechanism).
  - They inhibit **release of TSH** leading to ↓ **size and vascularity of the gland**.
- Improvement in thyrotoxic symptoms occurs within 2–7 days, but if therapy with iodides is continued (>2-4 weeks), the beneficial effects disappear and manifestations of hyperthyroidism reappear **(iodine escape).**

Adverse effects

- Iodides are secreted in saliva, nasal, and lacrimal secretions causing **metallic taste** and **irritation** of the salivary glands, mucous membranes and gastric mucosa. They increase lacrimal and nasal secretions.
- **Iodine escape** if used > 2-4 weeks.
- Iodides increase intraglandular stores of iodine, which may **impair** uptake of thiouracil drugs or radioactive iodine by the gland. So, during preoperative preparation, they must be given **after thiouracil drugs** (or radioactive iodine), **not before them**.
- Allergic reactions: skin rash, drug fever, etc.

Thyrotoxic crisis (thyroid storm)

It is a sudden severe exacerbation of the manifestations of thyrotoxicosis due to sudden release of T3 & T4 (medical emergency). It is a common postoperative complication if the patient was not well-prepared.

Manifestations
- High fever with vomiting and sweating.
- Tachycardia, arrhythmia, acute heart failure, and shock.
- Convulsions, coma, and even death from heart failure.

Management

- **Intravenous fluids** and **Paracetamol** to control dehydration and fever.

  N.B. Aspirin must be avoided, because salicylate displaces bound T4 and T3, and also because of its uncoupling effect on oxidative phosphorylation renders the metabolic state even more severe.

- **Propranolol** (1-2 mg slowly i.v. or 40 mg oral /6 h) to control arrhythmia.
  - **Esmolol** is a short-acting β-blocker can be also given by i.v.i.
  - If β-blockers are contraindicated give **diltiazem** by i.v. infusion.
- **Potassium iodides:** 10 drops orally/day to block hormone release and peripheral conversion of T4 to T3.
- **Propylthiouracil:** 250 mg/6 hrs orally to block hormone synthesis. It acts more rapidly than other thiouracil drugs.
- **Hydrocortisone:** 100 mg i.v./6-8 h to elevates BP and reduces toxemia. It also blocks peripheral conversion of T4 to T3.
- **Plasmaphoresis** in severe cases to reduce circulating thyroxin.

Management of myxedema coma

Myxedema coma is an end state of untreated hypothyroidism. There is progressive weakness, hypothermia, hypoventilation, hypoglycemia, hyponatremia, water intoxication, shock, and death. It carries high mortality and is a medical emergency.

Management

- **Hospitalization** (**ICU):** artificial respiration may be required.
- **L-thyroxine (T4):** 400 µg i.v. initially, followed by 50 µg daily orally. **Intravenous T3** can be used.
- **Hydrocortisone:** 100 mg i.v./ 6-8 h because the patient usually has associated adrenal insufficiency.
- **Intravenous fluids** with caution to avoid excessive volume overload.

Part 4: Adrenocortical Steroids

Classification:
- **Glucocorticoids:** have mainly anti-inflammatory action.
- **Mineralocorticoids:** have mainly Na & water retaining action.
- **Sex hormones:** are mainly anabolic.

Glucocorticoids

	Anti-inflam potency	Na^+ retention potency	Duration of effect
Short-acting glucocorticoids:			
Hydrocortisone (cortisol)	**1**	**1**	8-12 h
Prednisone and Prednisolone	4	0.5	
Methylprednisolone	5	0.1	
Intermediate-acting glucocorticoids:			
Triamcinolone	5	0.1	12-36 h
Paramethasone	10	0.01	
Long-acting glucocorticoids:			
Dexamethasone	30	0.01	48 h
Betamethasone	30	0.01	
Aldosterone:	0.3	3000	

- Hydrocortisone (cortisol) is the natural (endogenous) glucocorticoid.
- Equivalent dose means 20 mg of hydrocortisone = 5 mg of prednisolone.
- Steroids with high anti-inflam action *(e.g. dexamethasone)* are better used for inflammatory conditions e.g. **rheumatic fever**, while those with high Na & H_2O retention *(hydrocortisone)* are better used for treatment of hypotension and **shock** states (they also have rapid action).

Pharmacokinetics

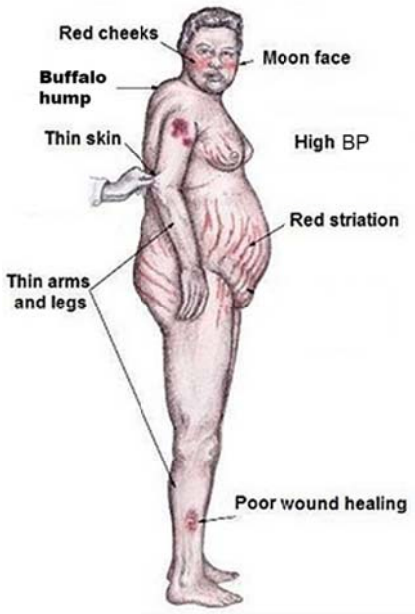
- All glucocorticoids are completely & rapidly absorbed by **all routes**.
- 80% of hydrocortisone is bound to plasma globulin, 10% to albumin.
- Plasma t ½ varies according to type (60-90 min for hydrocortisone). However, the effect of glucocorticoids is **prolonged** due to its effect on gene functions.
- Metabolism is by the liver and excretion is by the kidney.

Mechanism of action

Corticosteroids bind first to cell surface receptors then to cytoplasmic receptors

(carriers), then transported to the **nucleus**, where it interacts with many **DNA receptors** (steroid response elements) and affect their function.

Pharmacological effects:



- **On metabolism: (Cushing syndrome):**
  - Carbohydrate metabolism: hyperglycemia (↓ peripheral glucose utilization).
  - Protein metabolism: Catabolic effect → ↓ muscle mass and thin limbs.
  - Fat metabolism: ↑ lipolysis with redistribution of fat (moon face & buffalo hump).
  - On water and electrolyte balance: Na^+ & water retention and hypokalemia.
- **Anti-inflammatory and anti-immunological effects:**
  - They inhibit B cell function → ↓ antigen-antibody reaction.
  - They inhibit T cell functions → ↓ inflam mediators and cytokine release.
  - They inhibit macrophage activity and stabilize lysosomal membranes.
  - They inhibit mast cells → ↓ histamine release and capillary permeability.
  - They inhibit *phospholipase A2* enzyme → ↓ synthesis of PGs & LTs.
- **On CVS:** Hypertension due to:
  - Na^+ & water retention.
  - Increase sensitivity of BV and heart to circulating catecholamines.
- **Anti-shock effects:** due to:
  - Hypertensive and CVS effects (mention them).
  - Anti-inflammatory action (mention them).
- **Hematological effects:**
  - ↑ RBCs and neutrophils and ↓ lymphocytes and eosinophils.
  - ↑ coagulation factors and blood cholesterol.
- **On growth:** Growth retardation, which is not prevented by growth hormone.
- **On bone:** ↓ bone matrix and ↑ Ca^{2+} excretion (osteoporosis).

Administration

- Drug administration should follow the **circadian rhythm**: A double dose is given in the morning, and a single dose is given in the afternoon.

- **Alternate-day therapy** is clinically effective with minimal effect on the adrenal-hypothalamic-pituitary axis. In this therapy, double the dose of short- or intermediate-acting glucocorticoids is administered every other day.
- Glucocorticoids should be stopped **gradually** after long term administration.

Therapeutic uses

- **Inflammatory disorders:** e.g. iridocyclitis, neuritis, dermatitis, etc.
- **Autoimmune disorders:** e.g. vasculitis, rh fever, rh arthritis, hemolytic anemia, nephrotic syndrome, ulcerative colitis, etc.
- **Allergic disorders:** e.g. anaphylactic shock, urticaria, eczema, bronchial asthma, allergic conjunctivitis, etc.
- **Malignancy:** e.g. lymphoma, leukemias, multiple myeloma, etc.
- **Shock and hypotension…..Why?**
- **Organ transplantation:** as immunosuppressive to prevent graft rejection.
- **Cerebral edema:** dexamethasone is used after brain surgery to minimize inflammatory edema associated with tissue injury.
- **Acute hypercalcemia:** to enhance Ca^{2+} excretion.
- **As replacement therapy in acute and chronic adrenocortical insufficiency (Addison's disease).**

  N.B. Acute adrencortical insufficiency (acute Addisonian crisis):
  - Prolonged corticosteroid therapy produces feedback inhibition of ACTH and inhibition of endogenous cortisone secretion. When exogenous corticosteroids are suddenly stopped, severe hypotension and shock occurs.
  - Management:
    - i.v. fluids (saline).
    - Hydrocortisone 100 mg i.v./8h until the patient is stable.
    - ACTH: 0.5 mg i.m.

- **Stimulation of lung maturation in the fetus:**
  Lung maturation in the fetus is regulated by fetal secretion of cortisol. When delivery is anticipated before 34 weeks of gestation, **betamethasone** is given to reduce the incidence of respiratory distress syndrome in the infant. Betamethasone is chosen because its maternal protein binding is less than other steroids, allowing increased transfer across the placenta to the fetus.

Adverse effects

Most of these side effects occur after **long duration** of therapy:

- **Iatrogenic Cushing syndrome:** occurs if doses up to 100 mg hydrocortisone are used daily for > 2 weeks. It is characterized by moon face, buffalo hump, thin limbs, osteoporosis, hypertension, DM, edema, etc.
- **Immune suppression** leading to flaring of infections (especially viral and TB).
- **Hypertension** due to salt & water retention
- **Hyperglycemia.**
- **Peptic ulcer:** due to prolonged inhibition of gastroprotective PGs.
- ↑ **IOP (Glaucoma)**: due to ↓ aqueous humor drainage.
- **Osteoporosis.**
- **Growth retardation** in children.
- **Skin atrophy** & hypopigmentation after prolonged topical use.
- **Sudden withdrawal** after prolonged administration causes **acute addisonian crisis.**

Contraindications

- **Presence of infections:** especially viral infection and TB.
- **DM**.
- **Hypertension & heart failure:** they cause salt and water retention.
- **Peptic ulcer:** they ↓ synthesis of PGE_2 and I_2 that protect the stomach.
- **In early pregnancy:** may cause cleft palate.

N.B. Uses of corticosteroids in presence of T.B:
- TB meningitis: to prevent adhesions.
- TB of the suprarenal gland: to replace hypofunction.
- Miliary TB: to ↓ TB toxemia.

Mineralocorticoids

1. Natural mineralocorticoids: Aldosterone

Physiological actions: It binds to specific intracellular receptors in the DCT to inhibit Na^+ excretion (hypernatremia) and stimulates K^+ and H^+ excretion (hypokalemia).

2. Synthetic mineralocorticoids:

- **Deoxycorticosterone acetate (DOCA):** it has mainly mineralocorticoid effect.
- **Fluodrocortisone:** it has both gluco- and mineralocorticoid effects.

Part 5: Regulation of calcium metabolism (Bone mineral homeostasis)

1. Primary hormonal regulators of Ca^{2+} metabolism and bone mineral homeostasis:

Parathormone (PTH)	Calcitonin (CT)	Vitamin D
It is a single chain polypeptide secreted by the parathyroid glands. Its secretion is **not under pituitary control** but controlled by the level of serum Ca^{2+}.	It is a single chain polypeptide secreted by the C-cells of the thyroid. Its secretion is **not under pituitary control** but controlled by the level of serum Ca^{2+} and vitamin D.	It is fat-soluble vitamin found in **2** forms: ▪ **Vitamin D_2** (ergocalceferol): plants. ▪ **Vitamin D_3** (cholecalceferol): animals, and can be synthesized in human skin by the action of UV rays. The two forms must be activated by 2 OH at site **25** (liver) and **1** (kidney).
Mechanism and effects: PTH acts on specific receptors in bone and kidney leading to ↑ serum Ca^{2+} and ↓ PO_4 through: – **Bone:** ↑ bone resorption. – **Intestine:** ↑ Ca^{2+} absorption *(through activation of vit D).* – **Kidney:** ↑ Ca^{2+} reabsorption and PO_4 excretion.	**Mechanism and effects:** CT acts on specific receptors in bone and kidney leading to ↓ serum Ca^{2+} and PO_4 through: – **Bone:** ↓ bone resorption. – **Intestine:** ↓ Ca^{2+} absorption. – **Kidney:** ↓ reabsorption of Ca^{2+} and PO_4.	**Mechanism and effects:** Vit D acts on DNA receptors to synthesize proteins necessary for Ca^{2+} transport. – **Bone: the effect is complex:** when bone Ca^{2+} is deficient (rickets), vit D ↑ Ca^{2+} deposition (calcification) but excess vit D in normal subjects leads to bone resorption and hypercalcemia. – **Intestine:** ↑ Ca^{2+} absorption from the intestine. – **Kidney:** ↑ Ca^{2+} and PO_4 reabsorption.
Therapeutic uses:	**Therapeutic uses:**	**Therapeutic uses:**

Synthetic PTH **(teriparatide)** in low and intermittent doses may stimulate bone formation and can be used for **treatment of osteoporosis.**	Salmon CT (parenteral or intranasal) can be used for: ▪ Treatment of hypercalcemia and hyperphosphatemia. ▪ Treatment of osteoporosis. ▪ Treatment of Paget's disease of bone.	▪ Treatment of hypocalcemia and hypophosphatemia. ▪ Treatment of osteoporosis. ▪ Treatment of rickets (children) and osteomalacia (adults). **Drug interactions:** – Phenytion and phenobarbitone **(antiepileptic drugs)** stimulate hepatic microsomal enzymes → **↑ vitamin D metabolism**. So epileptic patients on long term therapy may develop osteomalacia or rickets. – Cholestyramine ↓ vitamin D absorption. – Thiazides ↑ the hypercalcemic effects of vitamin D.

2. Secondary hormonal regulators of Ca^{2+} metabolism and bone mineral homeostasis:

Glucocorticoids	Estrogen
▪ Prolonged administration of glucocorticoids can cause osteoporosis in adults and retarded growth in children due to **↑ renal Ca^{2+} excretion** and **↓ bone formation.** Also it antagonize intestinal vitD-stimulated Ca absorption ▪ Glucocorticoids can be used to **treat hypercalcemia** associated with lymphomas and sarcoidosis.	▪ Bone contains estrogen receptors. Estrogen administration ↑ blood levels of vitamin D and **↓ bone resorption**. ▪ Estrogen is used in the treatment of **postmenopausal osteoporosis,** but prolonged administration is not recommended because it may cause many side effects (e.g. breast cancer and endometrial carcinoma). ▪ **Selective Estrogen Receptor Modulators (e.g. Raloxifene)**, were developed to stimulate estrogen receptors in bones and block them in the breast and uterus (i.e. mixed agonist-antagonist).

3. Non-hormonal regulators of Ca^{2+} metabolism and bone mineral homeostasis:

Bisphosphonates (risedronate and zoldronic acid)	Thiazides	Fluoride
– They are analogs of pyrophosphate in which the P–O–P bond is replaced by the stable P–C–P bond. – After oral administration, all bisphosphonates have very poor (1–3%) oral absorption that is decreased by food. Recommendation is to administer on an empty stomach with a full glass of water and remain standing for 30 minutes. **Mechanism:** They inhibit many osteoclastic cell functions and induce cause **apoptosis** of osteoclasts. **Uses:** ▪ Treatment of hypercalcemia associated with malignancy and bone lesions associated with **bone metastasis.** ▪ Treatment of osteoporosis. ▪ Treatment of Paget's disease of bone and syndromes of ectopic calcification. **Side effects:** High doses can cause **renal impairment** and **osteonecrosis of the jaw.**	Thiazides are used to **decrease renal Ca^{2+} excretion** through ↑ the effect of PTH in stimulating renal Ca^{2+} reabsorption.	Fluoride is well-established for the prophylaxis of **dental caries** and is under investigation for the treatment of osteoporosis. Fluoride is accumulated in bones and teeth causing **stabilization of the hydroxyapatite crystal**.

Hypercalcemia

Causes: In over 90% of cases hypercalcemia is due to either **hyperparathyroidism** or **malignancy** (especially myeloma). Hypercalcemia normally suppresses PTH and so PTH is therefore the best first test to identity the cause of hypercalcemia.

Management of acute hypercalcemia

- Saline diuresis: 500-1000 ml/hour plus furosemide to increase urine flow and enhance Ca^{2+} excretion.
- Hydrocortisone: 100 mg i.v. to enhance Ca^{2+} excretion.
- Intravenous bisphosphonates.
- Hemodialysis especially when renal failure is present.

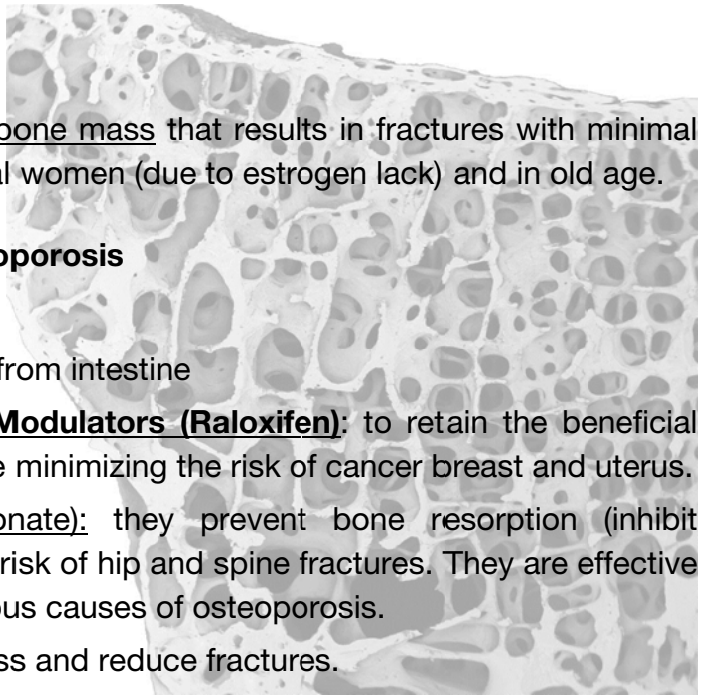
Hypocalcaemia

Causes: Hypoparathyroidism (N.B. tetany occurs when serum Ca^{2+} falls < 7mg/dl), chronic renal failure, vitamin D deficiency, etc.

Treatment

- Diet rich in calcium and low in phosphate
- Calcium gluconate: slowly i.v. (in acute conditions).
- Vitamin D: to ↑ Ca^{+2} absorption from intestine.
- Thiazide diuretics.

Osteoporosis



Definition: it is a condition of low bone mass that results in fractures with minimal trauma. It occurs in postmenopausal women (due to estrogen lack) and in old age.

Prevention and treatment of osteoporosis

- Diet rich in **calcium**.
- **Vitamin D**: to ↑ Ca^{+2} absorption from intestine
- **Selective Estrogen Receptor Modulators (Raloxifen)**: to retain the beneficial effects of estrogen on bone while minimizing the risk of cancer breast and uterus.
- **Bisphosphonates** (e.g. risedronate): they prevent bone resorption (inhibit osteoclastic activity) and reduce risk of hip and spine fractures. They are effective in both men and women for various causes of osteoporosis.
- **Calcitonin:** to increase bone mass and reduce fractures.
- **Teriparatide:** a recombinant form of PTH that has been recently approved for treatment of osteoporosis. It stimulates new bone formation and reduces risk of fractures.

- **Slow release fluoride preparation**: is a new treatment. It may reduce rates in postmenopausal osteoporosis.

Drug-induced osteoporosis

1. Corticosteroids.
2. Heparin.
3. Interferons.
4. Alum containing antacids.

Part 6: Sex Hormones

I. Estrogen

- **Natural estrogens:** estradiol, estrone and estriol
- **Semisynthetic estrogens:** Ethinyl estradiol and mestranol.
- **Synthetic estrogens:** diethyl stilbosterol.

Physiologic effects

- Normal development of genital tract and breast.
- Development of ♀ secondary sex characters.
- Metabolic effects:
  - Increase bone mass and prevent bone resorption.
  - Increase blood glucose and TGs.
  - Salt and water retention.
- Increase blood coagulation and platelet adhesiveness.

Therapeutic uses

- Contraceptive pills.
- Dysfunctional uterine bleeding.
- Replacement therapy in ovarian hypofunction.
- Postmenopausal symptoms e.g. atrophic vaginitis and osteoporosis.
- Cancer prostate.

Adverse effects and contraindications: see contraceptive pills.

II. Anti-estrogens:

1. Clomiphene citrate (Clomid)

- Clomiphene blocks estrogen receptors in hypothalamus and pituitary → ↑ FSH and LH → stimulate ovulation.
- It is used to **stimulate ovulation** in infertile women with normal pituitary function.
- **Adverse effects:** Ovarian enlargement and hot flushes.

2. Selective estrogen receptor modulators (SERMs):

- SERMs are ligands for the estrogen receptor that have agonist activity in one tissue but may have antagonist activity or no activity in another tissue.
- Currently, there are three SERMs: tamoxifen, raloxifene, and toremifene.

Tamoxifen

- It is an estrogen antagonist in the breast but is an agonist in the uterus and bone.
- It is used in the treatment of advanced, estrogen receptor positive **breast cancer** and for primary prevention of breast cancer in women at high risk.
- **Adverse effects:** tamoxifen increases the risk of endometrial cancer and thrombotic complications.

Raloxifene

- It is an agonist in bone but has no effect on the uterus or breast.
- It is used for the treatment and prevention of postmenopausal **osteoporosis**.
- **Adverse effects:** hot flashes and thrombotic complications.

3. Aromatase inhibitors:

- Aromatase is the enzyme that catalyzes the production of estrogens from androgenic precursors within the ovary and peripheral tissues.
- Aromatase inhibitors are a new class of oral estrogen synthesis inhibitors.
- **Anastrazole** and **letrozole (Femara)** are nonsteroidal competitive inhibitors of aromatase. **Exemestane** is a steroidal, irreversible aromatase inhibitor.
- These drugs are used for treatment of postmenopausal women with estrogen-receptor positive **breast cancer** who have received two to three years of tamoxifen and are switched to them for completion of a total of five years of adjuvant hormonal therapy.

II. Progesterone and progestins

- **Natural:** progesterone injection
- **Synthetic:** medroxy progesterone acetate.

Therapeutic uses

- Contraceptive pills.
- Dysfunctional uterine bleeding
- Dysmenorrhea and endometriosis.
- Threatened abortion.

Adverse effects

- Breakthrough bleeding.
- Increase risk of birth defects if given in early pregnancy.
- Liver dysfunction.

Antiprogesterone: Mifepristone

- It is a competitive blocker of progesterone receptors.
- It is used with $PGF_{2\alpha}$ to induce **medical abortion** in the first trimester.

III. Androgens and anabolic steroids

- **Natural androgens:** androsterone and testosterone
- **Synthetic androgens:** testosterone propionate.
- **Anabolic steroids:** nandrolone and stanazol.

Uses of androgens and anabolic steroids:

- Chronic debilitating diseases e.g renal failure.
- Chronic refractory anemia: e.g. sickle cell anemia, aplastic anemia.
- Illicit use by athletes: to increase muscle bulk and strength.

Adverse effects

- Reduction in spermatogenesis after stopping.
- Precocious puberty and premature closure of epiphysis in children.
- Cholestatic jaundice.
- Verilizing effects in females.

Contraindications

- Prostatic tumors (benign and malignant).
- Liver diseases
- Children.

Antiandrogens

1. 5 α-reductase inhibitors: Finasteride

- It inhibits ***5 α-reductase enzyme*** responsible for **conversion** of testosterone into the **active** form dihydrotestosterone (DHT).
- It is used in:

- Treatment of benign prostatic hyperplasia.
- Treatment of male baldness.
- Treatment of hirsutism in females.

2. Testosterone receptor blockers:

- **Cyproterone acetate:** is a competitive blocker of testosterone receptors. It is used in male hypersexuality, and hirsutism in females.
- **Flutamide:** used in cancer prostate.
- **Others: Spironolactone** is a competitive blocker of both aldosterone and testosterone receptors. It is used in hirsutism in females.

HORMONAL CONTRACEPTIVES

Types of hormonal contraceptives

- **Combined preparations** (the most effective type): contain both estrogen + progesterone given from the 5th day of menstruation for 21 days.
- **Single entity preparations:**
  - Progesterone alone (minipills): Don't affect lactation and don't carry risk of thrombosis but can cause uterine bleeding.
  - Estrogen alone (postcoital pills or morning-after pills): It is used within 72 hrs after sexual intercourse for 5 days.
  - Slow release progestins: Medroxyprogesterone acetate (Depo-Provera®) given i.m. every 3 months. It is suitable for unreliable women.
  - Implantable progestin preparation.

Mechanism of action

- They **inhibit ovulation** by exerting –ve feedback on LH (progesterone) and FSH (estrogen) secretion.
- Produce **endometrial changes** and interferes with **coordinated contraction** of the cervix, uterus, and fallopian tubes → ↓ sperm transport and fertilization.
- **Increase viscosity** of cervical mucus to inhibit sperm penetration.

Adverse effects

CVS: the most serious side effects especially in women above 35 years and in women who are smokers:

- Hypertension and increase risk of myocardial infarction.

- Thrombosis and thromboembolic catastrophes.
- Increase TGs levels.

CNS:
- Migraine headache.
- Cerebral hemorrhage (stroke) is 2-10 times higher.
- Mood changes and depression.

GIT:
- Nausea and vomiting.
- Cholecystitis and gall stones.
- Cholestatic hepatitis and hepatotoxicity.

Endocrinal:
- Hyperglycemia and DM.
- Weight gain and edema due to salt and water retention.
- Inhibition of lactation in lactating women.
- Menstrual irregularities: spotting bleeding, breakthrough bleeding, amenorrhea, and dysmenorrhoea.
- Loss of libido, acne, and hirsutism.

Cancer: increased risk of breast cancer.

Contraindications
- Hypertension or ischemic heart disease (IHD).
- History of embolism, thrombosis or cerebral hemorrhage.
- History of cancer breast or estrogen-dependent neoplasm.
- Migraine headache.
- Chronic liver disease and gall stones.
- Diabetes mellitus.
- Obese, smokers, or women over 35 years.
- Pregnancy.
- Depression.

N.B Causes of failure of contraceptive pills:
- If taken with **enzyme inducers** e.g. rifampin, phenytoin, etc.
- If woman taking **broad spectrum antibiotics** e.g tetracyclines *(see breakthrough pregnancy in general pharmacol).*
- **Paraffin oil** (laxative) ↓ intestinal absorption of contraceptive pills.

Part 7: Hypothalamic and Pituitary Hormones

ANTERIOR PITUITARY HORMONES

Growth hormone (GH)

GH promotes longitudinal bone growth and cartilage synthesis through stimulation of hepatic synthesis of **insulin-like growth factors** (somatomedins).

Therapeutic uses

- Replacement therapy in children with GH deficiency.
- Illicit use by athletes to increase body mass.

Adverse effects:

- Children may develop scoliosis during rapid growth.
- Peripheral edema and carpal tunnel syndrome.
- Hypothyroidism and gynecomastia.

Growth hormone antagonists: Octreotide

- It is a synthetic somatostatin analog.
- It is more potent and has longer duration than somatostatin.

Therapeutic uses

- Acromegaly.
- Hormone-secreting tumors (e.g. insulinoma, glucagonoma, gastrinoma, etc).
- Bleeding esophageal varices (given by i.v.i., it causes VC of splanchnic bl vessels and controls variceal bleeding with fewer side effects than vasopressin; see GIT).

Adverse effects: Bradycardia and conduction disturbances.

Adrenocorticotrophic hormone (ACTH)

ACTH is secreted by the pituitary to stimulate release of glucocorticoids, meniralocorticoids, and sex hormones. It also stimulates MSH → skin pigmentation.

Therapeutic uses

- To stimulate secretion of endogenous corticosteroids.
- Diagnostic: differentiation between 1^{ry} or 2^{ry} adrenal insufficiency.

Gonadotropin-releasing hormone (GnRH)

- GnRH is secreted by the hypothalamus to stimulate release of LH and FSH from anterior pituitary.
- **Pulsatile** injection of GnRH causes **stimulation** of LH & FSH but **continuous** infusion of GnRH causes **inhibition** of LH & FSH release.

Therapeutic uses

- Treatment of infertility caused by hypogonadism in both sexes by **pulsatile** injection of GnRH (to stimulate LH & FSH).
- Treatment of prostate cancer, endometriosis, and polycystic ovary syndrome by **continuous** administration of GnRH (to inhibit LH & FSH).
- In-vitro fertilization (IVF) programs.

Follicle-stimulating hormone (FSH)

Therapeutic uses

- Treatment of infertility caused by hypogonadism in both sexes.
- To stimulate ovulation as a part of in-vitro fertilization (IVF) programs.

Adverse effects

- Hyperstimulation syndrome (enlarged ovaries, ascites, fever, embolism, etc.)
- Gynecomastia in men.

Human chorionic gonadotropin (hCG)

It is glycoprotein produced by the placenta to stimulate ovarian corpus luteum to secrete progesterone (like LH). *h*CG can be used as LH substitute.

Therapeutic uses

- Treatment of infertility caused by hypogonadism in both sexes.
- To stimulate ovulation as a part of in-vitro fertilization (IVF) programs.
- Differentiation between undescended testes (cryptorchidism) and retracted testes (pseudo-cryptorchidism).

POSTERIOR PITUITARY HORMONES

Antidiuretic hormone (Vasopressin; ADH)

- It acts on 2 types of receptors: V1 and V2:
  - **V1:** present in **vascular** sm ms → VC and spasm.
  - **V2:** present in the **renal** collecting tubules → ↑ water reabsorption.

Therapeutic uses

- **Desmopressin:** synthetic long acting analog given by nasal administration in:
  - Diabetes insipidus (cranial type only): its action on renal V2 receptors is 3000 times more potent than on vascular V1 receptors.
  - Nocturnal enuresis: by reducing nighttime urine production.
  - Hemophilia: because it stimulates hepatic synthesis of factor VIII and endothelial cells to secrete von Willebrand factor.

- **Terlipressin** (Glypressin): used by i.v.i. to control acute variceal bleeding.
  Octreotide, vasopressin, and terlipressin have been shown to have efficacy in the control of acute variceal hemorrhage. **Terlipressin**, however, is the only medication that has been shown to improve patient survival.

Adverse effects

- Facial pallor and hypertension due to cutaneous VC.
- Coronary spasm.

Oxytocin

It causes **milk ejection** from the breast and **uterine contraction** at labor.

Therapeutic uses

- Induction and maintenance of labor (10-20 units by i.v.i).
- Control of postpartum hemorrhage.
- To stimulate milk secretion in nursing mothers (nasal spray)

Adverse effects and contraindications

- Rupture uterus in cephalopelvic disproportion (obstructed labor).
- Fetal asphyxia (from uterine spasm).
- Hypertension and cardiac arrhythmia

Notes

Clinical
Pharmacology
Department

Mansoura Faculty of Medicine

Review Questions

1. Classify types of **insulin**; mention its indications and side effects.
2. Classify types of **oral antidiabetic drugs**; mention their mechanism of action, indications and side effects.
3. Classify **antithyroid drugs;** mention their mechanism of action, side effects, and precautions of each group.
4. Classify **glucocorticoids**; mention their therapeutic uses, common side effects and contraindications.
5. Give full account on pharmacological regulation of **bone calcium homeostasis**.
6. Classify **oral contraceptives**; mention their mechanism of action, side effects and causes of failure.

Short questions:

1. Insulin resistance: definition, mechanism, and management.
2. Mention uses and side effects of sulfonylureas.
3. Mention drug interactions of oral hypoglycemic drugs.
4. Mention therapeutic uses and side effects of vasopressin.
5. Mention side effects (or contraindications) of oxytocin.
6. Mention drug interactions of vit D.
7. Mention treatment of osteoporosis.
8. Mention medical treatment of obesity.
9. Mention antiestrogens and their therapeutic uses.
10. Mention antiandrogens and their therapeutic uses.
11. Mention contraindications of anabolic steroids.
12. Mention side effects (or contraindications) of contraceptive pills.
13. Mention causes of failure of contraceptive pills.

Mention lines of treatment of the following emergency conditions:

1. Diabetic ketoacidosis.
2. Thyrotoxic crisis.
3. Myxedema coma.
4. Acute addisonian crisis.
5. Acute hypercalcemia.

Of each of the following questions, select ONE BEST answer:

1. Glucocorticoids are hormonal steroids:
A. Having an important effect on immune function
B. Having principally salt-retaining activity
C. Having androgenic or estrogenic activity
D. Having hypercalcemic activity
E. Having hyperkalemic activity

2. Correct statements about cortisol (hydrocortisone) include all of the following, EXCEPT:
A. Cortisol is synthesized from cholesterol
B. ACTH governs cortisol secretion
C. Most cortisol is inactivated in the liver
D. Cortisol has equal anti-inflammatory and salt-retaining activity
E. The half-life of cortisol in the circulations is normally about 60 hours.

3. Correct statements about glucocorticoids include all of the following, EXCEPT:
A. Effects of glucocorticoids are mediated by widely distributed glucocorticoid receptors that are members of the superfamily of nuclear receptors.
B. Glucocorticoids have high plasma protein binding
C. Glucocorticoids have dose-related metabolic effects on carbohydrate, protein, and fat metabolism.
D. Glucocorticoids have pro-inflammatory effects.
E. Glucocorticoids have catabolic effects in lymphoid and connective tissue, muscle, fat, and skin.

4. Which of the following glucocorticoids is relatively a short-acting drug?
A. Prednisolone
B. Dexamethasone
C. Triamcinolone
D. Paramethasone
E. Betamethasone

5. Which of the following glucocorticoids is an intermediate-acting drug?
A. Cortisone
B. Triamcinolone
C. Butamethasone
D. Prednisolone
E. Dexamethasone

6. Immunosupressive effect of glucocorticoids is caused by:
A. Reducing concentration of lymphocytes and inhibiting function of tissue macrophages and other antigen-presenting cells
B. Suppression of cyclooxygenase II expression which results in reducing amount of an enzyme available to produce prostoglandins
C. Activation of phospholipase A2 and reducing prostaglandin and leukotriene synthesis.
D. Activation of angiotensin-converting enzyme
E. Suppression of histamine release

7. Indication of glucocorticoids include of the following EXCEPT:
A. Chronic (Addison's disease) and acute adrenocortical insufficiency
B. Organ transplants (prevention and treatment of rejection – immunosuppression)
C. Inflammatory conditions of bones and joints (arthritis, bursitis, tenosynovitis).
D. Hypocalcemia
E. Gastrointestinal diseases (inflammatory bowel disease)

8. Indication for 1,25-dihydroxyvitamin D3 (calcitriol) administration is:
A. Vitamin D resistance
B. Elevated skeletal turnover
C. Hypercalcemia of malignancy
D. Hypophosphatemia
E. Primary hyperparathyroidism

9. Indication for risidronate administration is:
A. Failure of vitamin D formation in skin
B. Hypoparathyroidism
C. Elevated skeletal turnover
D. Hypophosphatemia

E. Metastatic bone disease

10. Correct statements about fluoride include all of the following, EXCEPT:
A. Fluoride is effective for the prophylaxis of dental caries
B. Fluoride is accumulated by bone and teeth, where it may stabilize the hydroxyapatite crystal
C. Subjects living in areas with naturally fluoridated water (1-2 ppm) had more dental caries and fewer vertebral compression fractures than subjects living in nonfluoridated water areas
D. Chronic exposure to very high level of fluoride results in thickening of the cortex of long bones and bony exostoses.

11. Which one of the following is most likely to be useful in the therapy of hypercalcemia?
A. Calcitonin
B. Glucocorticoids
C. 1-25 dihydroxy vitamin D3
D. Parenteral infusion of phosphate
E. Thiazide diuretics

12. Which of the following conditions is an indication for the use of calcitonin?
A. Chronic renal failure
B. Hypoparathyroidism
C. Intestinal osteodystrophy
D. Paget's disease of bone
E. Rickets

13. Which of the following drugs can cause rickets in children by increasing Vitamin D metabolism?
A. Tetracycline
B. Phenylbutazone
C. Phenytoin
D. Ciprofloxacin
E. Ibuprofen

14. Bone resorption is accelerated by:
A. Estrogens
B. Fluorides
C. Parathormone
D. Bisphosphonates
E. Calcitonin

15. Osteonecrosis of the jaw may be an adverse effect of:
A. Estrogens
B. Fluorides
C. Parathormone
D. Bisphosphonates
E. Calcitonin

16. Which of the following is an important effect of insulin?
A. Increased conversion of amino acids into glucose
B. Increased gluconeogenesis
C. Increased glucose transport into cells
D. Inhibition of lipoprotein lipase
E. Stimulation of glycogenolysis

17. Which of the following agents should be administered to achieve rapid control of the severe ketoacidosis in a diabetic boy?
A. Regular insulin
B. Glyburide
C. Insulin glargine
D. NPH insulin
E. Tolbutamide

18. Which of the following is the most likely complication of insulin therapy?
A. Dilutional hyponatremia
B. Hypoglycemia
C. Increased bleeding tendency
D. Pancreatitis
E. Severe hypertension

19. A 24-year-old woman with type 1 diabetes wishes to try tight control of her diabetes to improve her long-term prognosis. Which of the following regimens is *most* appropriate?
A. Morning injections of mixed insulin lispro and insulin aspart
B. Evening injections of mixed regular insulin and insulin glargine
C. Morning and evening injections of regular insulin, supplemented by small amounts of NPH insulin at mealtimes
D. Morning injections of insulin glargine, supplemented by small amounts of insulin lispro at mealtimes
E. Morning injection of NPH insulin and evening injection of regular insulin

20. Which one of the following drugs promotes the release of endogenous insulin?

A. Acarbose
B. Pioglitazone
C. Glipizide
D. Metformin
E. Miglitol

21. The combination of metformin and ethanol increases the risk of which of the following?
A. A disulfiram-like reaction
B. Excessive weight gain
C. Hypoglycemia
D. Lactic acidosis
E. Serious hepatotoxicity

22. Which of the following drugs is *most* likely to cause hypoglycemia when used as monotherapy in the treatment of type 2 diabetes?
A. Acarbose
B. Rosiglitazone
C. Glyclazide
D. Metformin
E. Miglitol

23. Which of the following drugs is taken during the first part of a meal for the purpose of delaying the absorption of dietary carbohydrates?
A. Acarbose
B. Exenatide
C. Glipizide
D. Pioglitazone
E. Repaglinide

24. The PPAR-γ receptor that is activated by thiazolidinediones increases tissue sensitivity to insulin by which of the following mechanisms?
A. Activating adenylyl cyclase and increasing the intracellular concentration of cAMP
B. Inactivating a cellular inhibitor of the GLUT2 glucose transporter
C. Inhibiting acid glucosidase, a key enzyme in glycogen breakdown pathways
D. Regulating transcription of genes involved in glucose utilization
E. Stimulating the activity of a tyrosine kinase that phosphorylates the insulin receptor

25. Which of the following patients is *most* likely to be treated with intravenous glucagon?
A. An 18-year-old woman who took an overdose of cocaine and now has a blood pressure of 190/110 mm Hg
B. A 27-year-old woman with severe diarrhea caused by a flare in her inflammatory bowel disease
C. A 57-year-old woman with type 2 diabetes who has not taken her glyburide for the last 3 d
D. A 62-year-old man with severe bradycardia and hypotension resulting from ingestion of an overdose of atenolol
E. A 74-year-old man with lactic acidosis as a complication of severe infection and shock

26. In Graves' disease, the cause of the hyperthyroidism is the production of an antibody that does which of the following?
A. Activates the pituitary thyrotropin-releasing hormone (TRH) receptor and stimulates TSH release
B. Activates the thyroid gland TSH receptor and stimulates thyroid hormone synthesis and release
C. Activates thyroid hormone receptors in peripheral tissues
D. Binds to thyroid gland thyroglobulin and accelerates its proteolysis and the release of its supply of T4 and T3
E. Binds to thyroid-binding globulin (TBG) and displaces bound T4 and T3

27. Methimazole reduces serum concentration of T3 primarily by which of the following mechanisms?
A. Accelerating the peripheral metabolism of T3
B. Inhibiting the proteolysis of thyroid-binding globulin
C. Inhibiting the secretion of TSH
D. Inhibiting the uptake of iodide by cells in the thyroid
E. Preventing the addition of iodine to tyrosine residues on Thyroglobulin

28. Though rare, a serious toxicity associated with the thioamides is which of the following?

A. Agranulocytosis
B. Lupus erythematosus-like syndrome
C. Myopathy
D. Torsades de pointes arrhythmia
E. Thrombotic thrombocytic purpura (TTP)

29. A 65-year-old man with multinodular goiter is scheduled for a near-total thyroidectomy. Which of the following drugs will be administered for 10–14 d before surgery to reduce the vascularity of his thyroid gland?
A. Levothyroxine
B. Liothyronine
C. Lugol's solution
D. Prednisone
E. Radioactive iodine

30. Which of the following is a sign or symptom that would be expected to occur in the event of chronic overdose with exogenous T4?
A. Bradycardia
B. Dry, puffy skin
C. Large tongue and drooping of the eyelids
D. Lethargy, sleepiness
E. Weight loss

31. When initiating T4 therapy for an elderly patient with longstanding hypothyroidism, it is important to begin with small doses to avoid which of the following?
A. A flare-up of exophthalmos
B. Acute renal failure
C. Hemolysis
D. Overstimulation of the heart
E. Seizures

32. A 27-year-old woman underwent near total thyroidectomy. She was started on levothyroxine. What hormone is produced in the peripheral tissues when levothyroxine is administered?
A. Methimazole
B. T3
C. T4
D. TSH
E. FSH

33. A 62-year-old woman presents with complaints of fatigue, sluggishness, and weight gain. She needs to sleep several times a day, which is unusual for her. She has been taking T4 for the past 15 yr without significant problems regarding her energy level. Her recent history is significant for diagnosis of arrhythmia, and she is currently taking an antiarrhythmic drug. What is the most likely cause of her current condition?
A. Amiodarone
B. Lidocaine
C. Procainamide
D. Sotalol
E. Verapamil

34. A 25-year-old woman presents with insomnia and fears she may have "something wrong with her heart." Lab tests confirm hyperthyroidism. Which of the following is a drug that produces a permanent reduction in thyroid activity?
A. ^{131}I
B. Methimazole
C. Propylthiouracil
D. Thiocyanate
E. Thyroglobulin

35. Glucocorticoids have proved useful in the treatment of which of the following medical conditions?
A. Chemotherapy-induced vomiting
B. Essential hypertension
C. Hyperprolactinemia
D. Parkinson's disease
E. Type II diabetes

36. A patient presents with pain and stiffness in his wrists and knees. The stiffness is worse first thing in the morning. A blood test confirms rheumatoid arthritis. You advise a short course of steroids. Which one of the following is the most potent anti-inflammatory steroid?
A. Cortisol
B. Dexamethasone
C. Fludrocortisone
D. Prednisone
E. Triamcinolone

37. A 34-year-old woman with ulcerative colitis has required long-term treatment with pharmacologic doses of a glucocorticoid agonist. Which of the following is a toxic effect associated with long-term glucocorticoid treatment?
A. A lupus-like syndrome
B. Adrenal gland neoplasm
C. Hepatotoxicity
D. Osteoporosis
E. Precocious puberty in children

38. Which of the following drugs is *most* useful for the treatment of hypercalcemia in Paget's disease?
A. Fluoride
B. Hydrochlorothiazide
C. Pamidronate
D. Raloxifene
E. Teriparatide

39. The active metabolites of vitamin D act through a nuclear receptor to produce which of the following effects?
A. Decrease the absorption of calcium from bone
B. Increase PTH formation
C. Increase renal production of erythropoietin
D. Increase the absorption of calcium from the GIT
E. Lower the serum phosphate concentration

40. Which of the following drugs is *most* likely to lower patient's serum PTH concentration?
A. Calcitriol
B. Cholecalciferol
C. Furosemide
D. Gallium nitrate
E. Risedronate

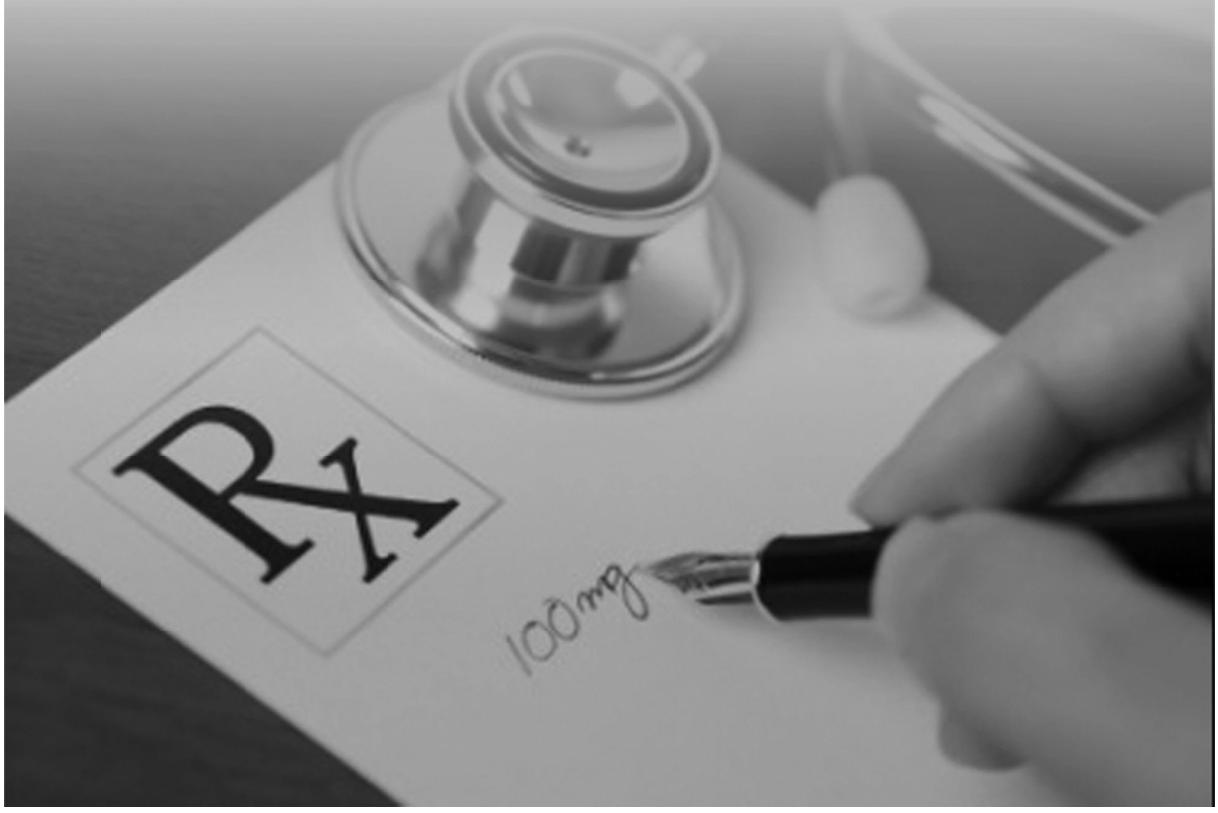
41. The patient began therapy with a nasal spray containing a protein that inhibits bone resorption. The drug contained in the nasal spray was which of the following?
A. Calcitonin
B. Calcitriol
C. Cinacalcet
D. Cortisol
E. Teriparatide

Answers

1 A	10 C	19 D	28 A	37 D
2 E	11 B	20 C	29 C	38 C
3 D	12 D	21 D	30 E	39 D
4 A	13 C	22 C	31 D	40 A
5 B	14 C	23 A	32 B	41 A
6 A	15 D	24 D	33 A	
7 D	16 C	25 D	34 A	
8 D	17 A	26 B	35 A	
9 E	18 B	27 E	36 B	

Chapter 10

CNS Pharmacology



Chapter 10

CNS Pharmacology

Part 1: CNS Stimulants

Classification:

1. **Respiratory stimulants** theophylline, nikethamide
2. **Psychomotor stimulants** amphetamines, antidepressants
3. **Psychotomimetic drugs** LSD, cannabis
4. **Spinal cord stimulants** strychnine

RESPIRATORY STIMULANTS (ANALEPTICS)

Definition: drugs that stimulate the depressed respiratory center (RC).

Classification:

- **Specific analeptics:**
  - Naloxon and nalorphine → used to treat opiates respiratory depression.
  - Flumazenil → used to treat benzodiazepines toxicity.
- **Non-specific analeptics:**
  - Direct RC stimulation: e.g. Xanthines (caffeine, theophylline) – Ethamivan - Heptaminol. They antagonize the GABA-mediated RC depression.
  - Indirect RC stimulation (reflex): e.g. Nicotine and lobeline. They stimulate RC indirectly through stimulation of the chemoreceptors in the carotid body.
  - Both (direct and indirect): Nikethamide - Doxapram

Therapeutic uses: all cases of RC depression (postanaesthetic, CNS depressants, COPD and some premature babies)

Adverse effects

- Tachypnea, tachycardia and hypertension.
- High doses can cause convulsions.

Contraindications

- Epilepsy (to avoid CNS stimulation).
- Severe hypertension, arrhythmia or IHD (to avoid cardiac arrhythmia).
- Thyrotoxicosis.
- Severe bronchial asthma.

PSYCHOMOTOR STIMULANTS

Definition: drugs that induce **euphoria** with **increased motor activity.**

Classification

- **Amphetamine and related drugs:** see ANS
- **Cocaine**
  - Cocaine inhibits tissue uptake of catecholamines.
  - Behavioral effects of cocaine are very similar to amphetamine.
  - Cocaine is used topically as a local anesthetic eye drops.
- **Xanthines:** see respiratory pharmacology.
- **Antidepressants:** see later.

PSYCHOTOMIMETIC DRUGS (HALLUCINOGENS)

Definition: drugs that affect **thought, perception** and **mood** with no effect on motor activity. They have **no clinical applications** but important for **drug abuse.**

Examples and Mechanisms

- **LSD (Lysergic acid diethylamide):** It stimulates central **5-HT** receptors and affects catecholamine action → severe hallucinations and delusions resembling acute **schizophrenia**.
- **Cannabis (hashish, marijuana):** It acts on cannabinoid receptors in the CNS (**CB_1**) causing loss of judgment of time & place and dream-like state. **I**t does not cause physical dependence but psychological dependence. **CB_2** receptors are found in peripheral tissue and immune system.
- **Phencyclidine:** It stimulates **δ-opioid** receptors and blocks the NMDA receptors and may interact with other neurotransmitter systems.

Part 2: Analgesics

Definition: drugs that relieve or decrease pain sensation.

Classification of analgesics:

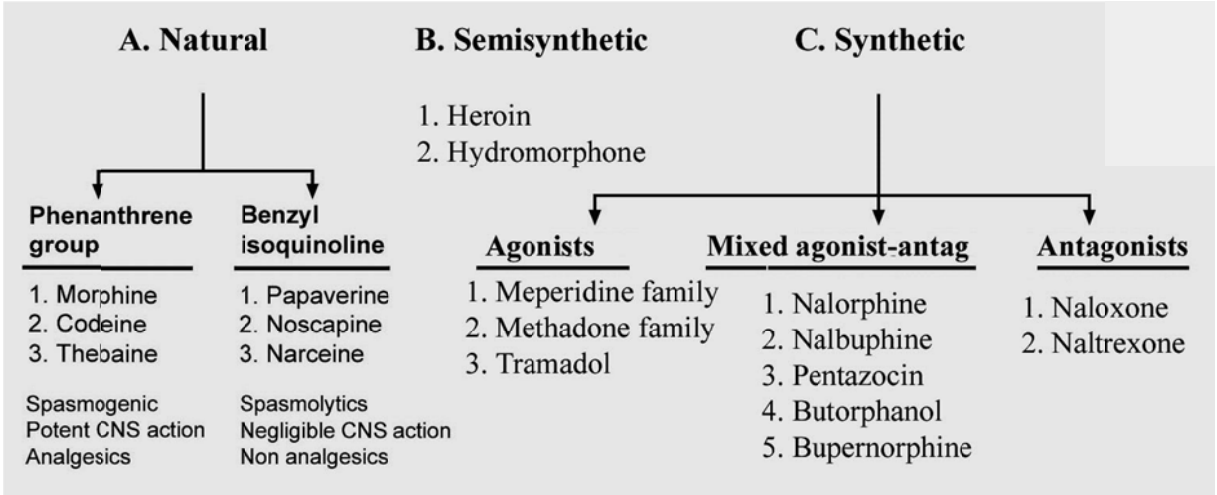
- **Opioid (narcotic) analgesics**
- **NSAIDs** (see chapter 4)**.**
- **Analgesic antipyretics:** e.g. paracetamol, Dipyron & Nefopam.
- **Drugs used for specific painful conditions** e.g. carbamazepine for trigeminal neuralgia, ergotamine for migraine.

OPIOID ANALGESICS

- They are drugs that decrease pain sensation without loss of consciousness and can induce physical dependence.
- **Opiates:** are drugs derived from opium plant (*Papaver sominiferum*). They include mainly morphine, codeine and papaverine.
- **Opioids:** are drugs with morphine-like activity.
- **Opiopeptins:** are endogenous peptides with opioid-like activity e.g. endorphins & enkephalins
- **Narcotics:** are drugs that produce narcosis i.e. drowsiness or stupor, with analgesia (stupor means marked impairment, but not complete loss of consciousness). These drugs are usually addictive. It is a **legal**, not a medical, term.

Papavar somniferum

Classification of opioid drugs



Mechanism of action

- Opioids such as morphine are believed to interact with three major receptors **(μ, δ, κ)**. Each opioid receptor has distinct subtypes (e.g., μ1, μ2). All three major receptors are present in high concentrations in the dorsal horn of the spinal cord.
- Interaction with **μ-receptors** contributes to supraspinal and spinal analgesia, respiratory depression, sedation, euphoria, decreased GI peristalsis, and physical dependence (addiction).
- The significance of interaction with **κ-receptors** is unclear, but it may contribute to analgesia (through inhibition of release of substance P at dorsal horn).

NATURAL OPIOID AGONISTS

1. Morphine

Pharmacokinetics

- **Oral absorption:** good (bioavailability is 25% due to significant first-pass effect). However, the analgesic effect is greater when the drug is administered parentrally
- **t½ :** 4-5 hrs.
- **Metabolism:** in the liver by conjugation leading to inactive metabolites.
- **Excretion:** renal (90%) – bile (10% as conjugated morphine).

Pharmacological effects

- **Analgesia**
  - **Dose-dependent analgesia (sensory & emotional):** consciousness is not lost and the patient can still locate the source of pain. Analgesia may be associated with **euphoria** and decreased anxiety.
  - Analgesia results from direct activation of **μ** and **δ** receptors in the spinal cord and possibly higher centers (thalamaus) leading to:
    - Activation of descending inhibitory pathways.
    - ↓ release of substance-P in pain transmission neurons in the spinal cord.
  - The psychic effect results from ↓ **NA release** in some CNS areas leading to decrease anxiety and reaction of the patient to pain.
  - Morphine and other exogenously administered opioids may also have some action on **peripheral** inflamed tissue.

N.B. Morphine can treat all types of pain **except itching. Why?**
a) Because morphine stimulates **histamine release** → ↑ itching.
b) Itching is different from pain sensation and has different receptors and centers.

- **Euphoria** (large doses produce dysphoria).
- **Miosis:** due to central stimulation of Edinger-Wistphal nucleus. **Severe miosis** is indicative of toxic doses.
- **Respiratory center depression**. This RC depression leads to CO_2 retention and cerebral VD → ↑↑ **intracranial tension.**
- **Cough suppression.**
- **Vagal stimulation.**
- **Nausea & vomiting:** due to stimulation of chemoreceptor trigger zone (CTZ).

CVS effects:

- **Orthostatic hypotension:** due to (a) Histamine release; (b) vagal stimulation.
- **Bradycardia:** due to vagal stimulation.

Smooth ms (Spasmogenic effects):

- **Bronchoconstriction:** due to: (a) Vagal stimulation. (b) Histamine release**.**
- **Constipation:** due to (a) spasmodic non-propulsive contractions of intestinal smoothms& decreased peristalsis; (b) ↑ intestinal water absorption.
- Spasm of the **sphincter of Oddi** → ↑ biliary pressure.
- **Feeling of urgency with difficult micturition** due to ↑ detrusor muscle tone with spasm of the internal urethral sphincter.
- **Uterus:** prolongation of labor by unclear mechanism.

Therapeutic uses

- **Analgesia:** for severe pain e.g. acute MI, cancer, surgery, etc.
- **Acute pulmonary edema (cardiac asthma).Why?**
  - ↓ stress & anxiety of the patient.
  - Venodilatation → ↓ VR & preload → ↓ pulmonary congestion.
  - Decrease tachypnea caused by the CNS response to hypoxic drive (due to its depressant effect on RC).
- **In anesthesia:**
  - As adjuvant to anesthetic agents (preanesthetic medication).
  - Regional anesthesia (epidural) to achieve long lasting analgesia by its effect on the spinal cord.
- **In severe colic:** (**morphine combined with atropine**). **Why?**
  - Because morphine is spasmogenic and atropine is spasmolytic.
  - To counteract muscarinic effects caused by excessive vagal stimulation (e.g. bronchoconstriction and bradycardia).

Preparations and doses

- Morphine sulphate: 10 mg s.c. or i.m. In acute MI it is given **5 mg i.v.**
- Intrathecal (epidural) injection: produce long lasting analgesia which is useful for critically ill patients at risk of RC depression.
- Sustained release preparations &transdermal patches are available.

Adverse effects:

CNS
- **Tolerance & physical dependence** (addiction) with prolonged use:
  - Physical dependence can occur within 24 h if given /4 h.
  - Tolerance may occur to analgesia and euphoria but not to respiratory depression.
- ↑↑ intracranial tension.
- **RC depression:** the most important effect and is dose-dependent.

Resp
- Bronchoconstriction.

CVS
- Postural hypotension

GIT
- Nausea, vomiting, and constipation.
- Increased biliary tract pressure and biliary colic.

Genito-Urinary
- Urine retention especially in patients with **enlarged prostate**.
- Prolongation of labor.

Eye
- Miosis is a consistent finding in morphine addiction.

Contraindications & precautions

- **Head injury & increased intracranial pressure**: Morphine causes respiratory depression & CO_2 retention. The ↑ CO_2 causes cerebral VD and ↑ intracranial tension.
- **Respiratory depression.**
- **Bronchial asthma:** Morphine causes bronchoconstriction due to (a) vagal stimulation; (b) histamine release. It also causes RC depression.
- **Biliary colic & gallstones:** due to spasm of the sphincter of Oddi → ↑ biliary pressure.
- **Senile enlarged prostate:** Morphine ↑ detrusor muscle tone with spasm of the internal urethral sphincter → feeling of urinary urgency with difficult micturition.
- **Hypotension and hypovolemia:** because morphine causes postural hypotension.
- **Hepatic damage:** Due to: (a) morphine is metabolized by the liver; (b) morphine increases the risk of hepatic encephalopathy due to marked CNS depression.
- **Hypothyroidism and adrenal insufficiency** (Addison's disease). **Why?**
  Because those patients have prolonged and exaggerated response to morphine.

- **Undiagnosed acute abdominal pain:** Morphine masks the pain (which may be dangerous e.g. appendicitis) and interferes with the correct diagnosis.
- **Infants and old patients:** are more susceptible to respiratory depression.

Chronic opioid toxicity (addiction)

- There are behavioral changes, constipation, itching &miosis.
- Sudden withdrawal (abstinence syndrome):
  - *Consists of:* irritability, nervousness, tremors, hypertension & ms cramps starts after 6-10 hrs from the last dose - peak effect at 48 hrs - gradually subsides over 5-10 days.
  - *Mechanism:* chronic administration of opioids ↓↓ endogenous production of endorphins and NA. Following sudden withdrawal, there is an immediate deficiency of endogenous opioids with rebound ↑ of NA release.

Treatment of chronic morphine addiction:

- Gradual withdrawal of morphine with substitution by **methadone,** then gradual withdrawal of methadone.
- **Clonidine:** to stimulate central α2 receptors and ↓ NA release.
- Sedatives: e.g. diazepam.

Acute opioid toxicity

Manifestations:

- Coma with depressed respiration, miosis, and shock.
- Death occurs from respiratory depression.

Treatment:

- Gastric lavage.
- Establish a patent airway and artificial respiration if needed.
- Opioid antagonists:
  - **Naloxone:** pure opioid antagonist and can reverse RC depression within minutes (0.4 - 0.8 mg i.v. for 2-3 doses).
  - **Nalorphine:** it is mixed agonist-antagonist (partial blocker).

N.B.
Opioid blockers are **indicated** in **acute** morphine toxicity but they are absolutely **contraindicated** in **chronic** morphine addiction because they precipitate severe withdrawal syndrome.

N.B.

- The duration of opioid antagonists is **shorter** than morphine. The patient should be watched carefully because he may go back into coma.
- Care should be taken to avoid **withdrawal** syndrome.

2. Codeine

Similar to morphine with the following differences:

- Has **greater oral bioavailability** (60%) due to **less first-pass effect**.
- The **analgesic** potency is **20%** of morphine, but more potent **cough** suppressant
- It has **little euphoric** effect.
- Most of the systemic effects of codeine are due to conversion in the liver into morphine by *demethylation* (codeine is *methylmorphine*).

Therapeutic uses

– Analgesic for mild to moderate pain (usually combined with paracetamol).
– As central antitussive (see chapter 7).

Adverse effects: (less than morphine)

– Constipation
– RC depression and addiction liability but it is fewer than morphine.

	Morphine	Codeine
Oral bioavailability:	25%	60%
Analgesic effects:	Strong	Weak (20%).
Antitussive effect:	Weak	Strong
Uses:	Mention its 4 uses	Analgesic and antitussive

SYNTHETIC AND SEMISYNTHETIC OPIOID AGONISTS

1. Heroin and hydromorphone

- They are semisynthetic opioids (heroin is diacetylmorphine).
- They are **more potent** than morphine but with rapid onset and shorter duration.
- They are **not used clinically** because they are **highly addictive.**

2. Meperidine (Pethidine)

Synthetic opioid similar to morphine with the following differences:

- **Better absorbed** orally and has **greater bioavailability** than morphine.
- The **analgesic** potency is **10%** of morphine.
- It is used as analgesic alternative to morphine in the following cases:
  - **Inferior MI** because in this case the patient usually has bradycardia.
  - It is preferred than morphine **during labor** because it has short duration and doesn't prolong labor (little or no spasmogenic action).

Adverse effects

- It causes **RC depression** and **addiction liability** but weaker than morphine.
- It causes **histamine release** and **bronchoconstriction**
- It has weak **atropine-like actions** → dry mouth, tachycardia, etc.
- It has **No** GIT, **No** antitussive, and **No** vagal stimulant effects.

	Morphine	Meperidine
Chemistry	Natural opioid	Synthetic opioid
Bioavailability	25%	Greater (50%)
Analgesic effect	Strong	Weak (10% of morphine)
Spasmogenic effects	Present	Absent
Autonomic effects	Vagal stimulation	Atropine-like action
Uses	Mention its 4 uses	Analgesic only

3. Fentanyl and alfentanil

- They are synthetic derivatives of meperidine**.** They are the **most potent** and the **shortest duration** opioid agonists.
- They are used as analgesic in **severe pain** (as long-acting transdermal **skin patch**). A transdermal fentanyl 12 microgram patch equates to approximately 30 mg oral morphine daily.

4. Methadone

Synthetic opioid similar to morphine with the following differences:

- The analgesic effect is **equal** to morphine**.**
- Has **longer duration** of action than morphine ($t_{1/2}$ is 24h)**.**

Uses:

- As analgesic.
- **Treatment of chronic opiate addiction and heroin users**:
  - It can satisfy the craving needs of the patient with less addictive features.
  - Methadone withdrawal symptoms are less severe than other opioids.

5. Tramadol

- It has two different mechanisms. First, it binds to the **μ**-opioid receptor. Second, it inhibits the reuptake of serotonin and NA.
- **Uses:** as **analgesic** for moderate to severe pain, especially musculoskeletal pain
- **Adverse effects:** It has relatively fewer side-effects than most opioids (but **addiction** can occur). It may induce **seizures** in epileptic patients.

6. Diphenoxylate and loperamide (see chapter 8)

SEMISYNTHETIC MIXED AGONISTS-ANTAGONISTS (partial agonists)

Nalorphine – Nalbuphine – Pentazocin – Butorphanol

- All these drugs have **agonist** activity on κ receptors and **antagonist** or **partial agonist** activity on μ receptors.
- They are used as **analgesics** alternative to morphine but their analgesic activity and respiratory depression are **less marked** than morphine.
- All these drugs (except nalbuphine) increase systemic and pulmonary vascular resistance leading to ↑ **cardiac load,** so they are, thus, **contraindicated to relieve pain of acute MI.**
- They can lead to **withdrawal symptoms** if given to opioid **addict** patients.

N.B.

For opioid analgesics, **potency** of the analgesic should be considered **more important** than efficacy because respiratory depression is dose-dependent.

SYNTHETIC FULL ANTAGONISTS

Naloxone and naltrexone

- They are competitive **blockers of all** opioid receptors.
- Naloxone is given **i.v.** and has short t½ (~1h) but naltrexone could be administered orally and has longer t½ (~48 h).
- They can precipitate **severe withdrawal** syndrome if administered to opioid-addict patient.

Therapeutic uses of naloxone

- **Acute opioid toxicity:** given i.v., the adverse respiratory and CVS effects of opioids are reversed within 1-2 min and lasts for 1-2 hrs.
- It is given during labor to mothers who received opioids **to prevent neonatal respiratory depression,** or it can be given to the neonate via the umbilical vein.

NON-OPIOID ANALGESICS

1. Acetaminophen (Paracetamol)

Pharmacokinetics

- Absorption is complete and rapid from GIT with peak levels after 30 min.
- Metabolism: liver by conjugation. At high doses, it is converted into **toxic metabolite** *(N-acetyl-benzoquinone)* that is responsible for hepatotoxicity.
- Excretion: mainly renal.

Mechanism & Pharmacological effects

- It is a **selective Cox III inhibitor** so it inhibits PGs synthesis in the brain only and has **analgesic & antipyretic** actions **without** effects on the enzymes that are responsible for synthesis of peripheral PGs and so it has **no anti-inflammatory action.**
- It has **little or No** effects on the CVS, GIT, respiratory or platelet functions.

Therapeutic uses

As analgesic and antipyretic **when aspirin is contraindicated** (e.g. patients with peptic ulcer, hemophilia, etc). Acetaminophen can be administered in **pregnancy** with greater safety than aspirin.

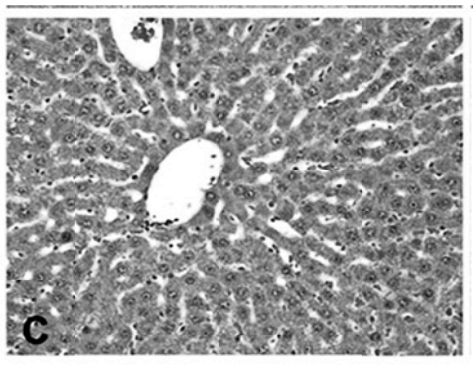
Adverse effects

- **At therapeutic doses:** acetaminophen is well-tolerated but may cause:
  - Skin rash& drug fever (as allergic reactions).
  - Long term use may lead to renal failure.

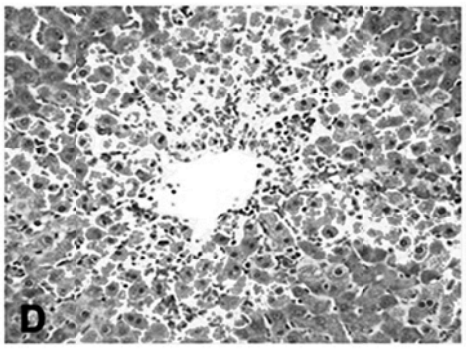
- **In toxic doses: dose-dependent hepato-toxicity** (centrilobular necrosis): It occurs with large doses (about **15 gm** in adults and **4 gm** in children)

  Mechanism of hepatotoxicity

  - Acetaminophen is converted to toxic metabolite *(N-acetyl-benzoquinone)* in the liver that needs detoxification by reduced **glutathione**.



Normal liver section



Hepatic cell necrosis
caused by acetaminphen toxicity

- When glutathione store is depleted, the toxic metabolite binds covalently to cellular proteins producing hepatocellular damage.
- Clinical symptoms of toxicity (e.g. vomiting) occur within 24 hrs but signs of hepatic damage (e.g. jaundice) occur after 2-6 days.

Treatment of toxicity

- **G**astric lavage with activated charcoal.
- **Sulfhydryl donors (acetylcysteine)** to restore hepatic glutathione. It must be started within **8** hours of toxicity.
- **Hemodialysis:** better within the first 12 hrs after ingestion.

The 20 hour IV protocol of acetylcysteine

- First, administer an initial loading dose of **150** mg/kg IV over 60 minutes.
- Next, administer **12.5** mg /kg per hour IV for 4 hours.
- Finally, administer **6.25** mg /kg per hour IV for 16 hours.

Nefopam (Acupan)

Mechanism and effects

- It is a **central analgesic** without antipyretic or anti-inflammatory activity. It is more potent than NSAIDs.
- The analgesic mechanism is **unclear** but may be related to inhibition of many transmitters reuptake or blocking central voltage-gated Na^+ channels.
- Nefopam is also used to combat severe **hiccups**.

Adverse effects

- Precipitation of epileptic convulsions in patients with epilepsy.
- Weak atropine-like actions: dry mouth, urine retention, etc.

Contraindications: history of epilepsy

Dipyrone (Novalgin)

Mechanism and effects

- **Analgesic antipyretic** that is more potent than aspirin. It has no anti-inflammatory action.
- Its use was restricted in many countries because of risk of **agranulocytosis** which is **not** dose-dependent.

Adverse effects

- **A**granulocytosis: reversible in 10 days after stoppage of the drug but lethal in 10% of cases.
- **A**llergic reactions and anaphylaxis.
- It can trigger bronchoconstriction in patients with **A**sthma.

Part 3: Sedative-Hypnotic Drugs

- These are drugs that cause sedation and relieve anxiety (anxiolytics), or can induce sleep. They are used primarily to treat anxiety and insomnia.
- Because there is considerable chemical variation within the group, these drugs are classified based on their clinical uses rather than on chemical structure.

Drugs with main use as sedatives:	Drugs with main use as hypnotics:
▪ Benzodiazepines ▪ Buspirone	▪ Barbiturates ▪ Ramelteon ▪ Chloral hydrate

1. Benzodiazepines

- Benzodiazepines (BDZ) have a **great margin of safety** over previously available sedative–hypnotic agents (e.g., barbiturates).
- Most benzodiazepines have qualitatively similar therapeutic actions but differ in their relative lipid solubility, metabolism, and elimination half-life.

Classification

- **Short acting (t½ < 5h):** midazolam – triazolam
- **Intermediate acting (t½ 5-24 h):** alprazolam – lorazepam - clonazepam
- **Long acting (t½ > 24 h):** diazepam – clorazepate - flurazepam

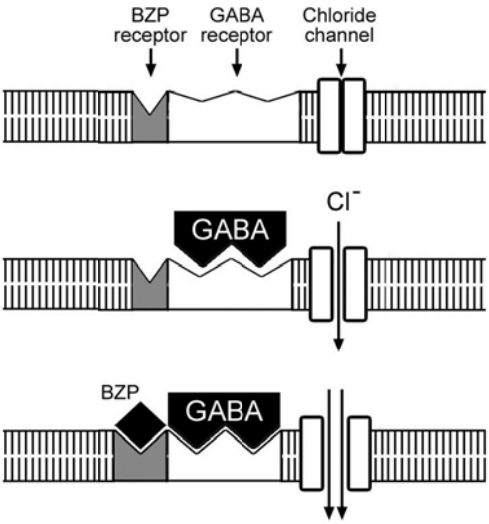
Pharmacokinetics

– Oral absorption is good and rapid. Highly lipid soluble drugs (e.g., midazolam, triazolam) have fast onset of action.
– Long acting drugs are metabolized by **oxidation** (CYP450) into **active** metabolites giving them long duration of action (e.g. diazepam).
– Short acting drugs are metabolized by **conjugation** into **inactive** metabolites followed by renal clearance.
– In a patient with liver dysfunction, **lorazepam** and **oxazepam**, which are metabolized **extrahepatically**, are less likely to cause excessive CNS depression.

Mechanism of action

- BDZ have special receptors in the CNS and peripheral tissue.
- By acting on these receptors, BDZ cause allosteric modulation of GABA action on $GABA_A$ receptors resulting in ↑ Cl- conductance and hyperpolarization.
- Six BDZ receptor subtypes have been discovered; **subtype 1** is the most widely expressed and mediates most of the effects of BDZ.

Pharmacological effects



- **Reduction of anxiety** (anxiolytic effect) in small dose producing calming effect in man & taming effect in animals
- **Hypnotic effect:** in higher doses.
- **Central skeletal muscle relaxation:** this is useful since increased ms tone is a common feature in anxiety and may lead to headache and ms pain.
- **Anticonvulsant effect.**
- **Acute amnesia:** after high doses.

Therapeutic uses

- **Anxiety disorders: e.g.**
  - Acute anxiety.
  - Generalized anxiety disorders (GAD).
  - Social phobia (social anxiety disorder).

  BDZ are effective for the **short-term** management (<6 weeks**)** of these anxiety disorders (*selective serotonin-reuptake inhibitors [SSRIs; see later] are now considered the first-line choices for the **long-term** management of anxiety disorders.*

- **Insomnia:** BDZ that have a rapid onset and sufficient duration are widely used (e.g., temazepam).

- **Anticonvulsants: Lorazepam** (and **diazepam**), given by i.v. may be used for initial treatment of status epilepticus and drug-induced seizures. The development of tolerance precludes their long-term use.

- **Short surgical procedures:** Shorter acting benzodiazepines (e.g., **midazolam**) are preferred before during surgery or endoscopy.

- **Preanesthetic medication.**

Adverse effects

- **Sedation, memory disturbance, dull attention** (interfere with learning ability).
- **Tolerance and physical dependence** (treated by gradual withdrawal).
- **Rebound insomnia** after discontinuation.
- **Hangover:** a state of psychomotor depression occurs in the following day after the use of long acting drugs (i.e. residual effect).
- **Apnea** after rapid i.v. injection *(flumazenil is the antidote)*

Flumazenil

Flumazenil is a **competitive antagonist** at benzodiazepine receptors. It is used to prevent or reverse the CNS effects from benzodiazepine overdose or to speed recovery from the effects of benzodiazepines used in anesthetic and diagnostic procedures.

Precautions: avoid BDZ use in the following conditions:

- Drivers and machine workers needing high attention.
- Pregnancy and lactation: fetal muscular hypotonia and impaired suckling may occur.
- Hepatic encephalopathy.
- Respiratory depression.
- Combination with other CNS depressants e.g. alcohol.

2. Buspirone

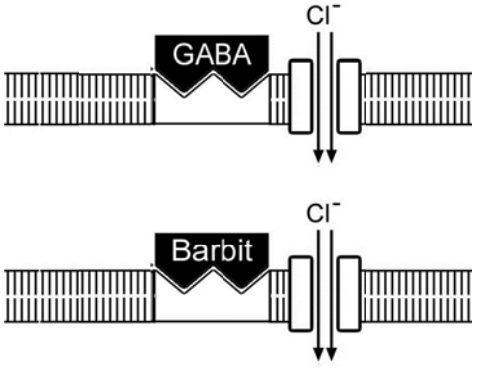
- It is partial agonist on **5-HT$_{1A}$** receptors in the midbrain.
- Selective anxiolytic without hypnotic or muscle relaxant effect.
- It suppresses anxiety after a long delay (2 or more weeks).
- It is the anxiolytic of choice in the elderly.
- No liability for drug dependence.
- **Adverse effects** include dizziness, headache, tachycardia and nervousness.

3. Barbiturates

- Barbiturates have been largely **replaced** by the more safe benzodiazepines and the SSRIs, for the treatment of anxiety and sleep disorders.
- **Phenobarbital** is a long acting barbiturate (~6-8h) used as an **anticonvulsant**; **thiopental** is ultrashort agent (~15-20 min) used as an i.v. **general anesthetic**.

Mechanism of action

- Barbiturates have either GABA-like action OR enhance the effects of GABA at GABA$_A$ receptors resulting in ↑ Cl- conductance and hyperpolarization.
- The action of barbiturates is non-selective i.e. increasing the dose of barbiturates → generalized CNS and **medullary depression**.

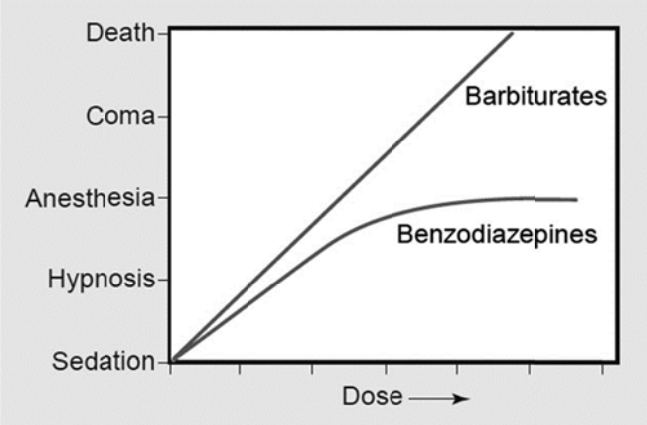


Therapeutic uses

- As sedative and hypnotics in the treatment of insomnia. They are largely replaced by benzodiazepines.
- **Phenobarbital** is used in the treatment of grand mal epilepsy.
- **Phenobarbital** is microsomal enzyme inducer. It is used in the treatment of hyperbilirubinaemia in neonates (physiological jaundice) to activate liver enzymes (glucuronyl transferase) and fasten metabolism of bilirubin.
- **Thiopental** is used as short i.v. anaesthetic in short procedures.

Adverse effects

- Physical dependence.
- **Respiratory** and **myocardial depression** (in acute toxicity)
- Phenobarbital is hepatic microsomal enzyme inducer.
- Phenobarbital may increase **porphyrin** synthesis. It can precipitate the symptoms of acute intermittent porphyria.



4. Ramelteon

- Ramelteon is prescribed for patients who have difficulty falling asleep. It is a selective agonist at **melatonin MT1** and **MT2** receptors that are involved in the promotion of sleep and that maintain the normal circadian rhythm.
- **Adverse effects** include dizziness and fatigue.

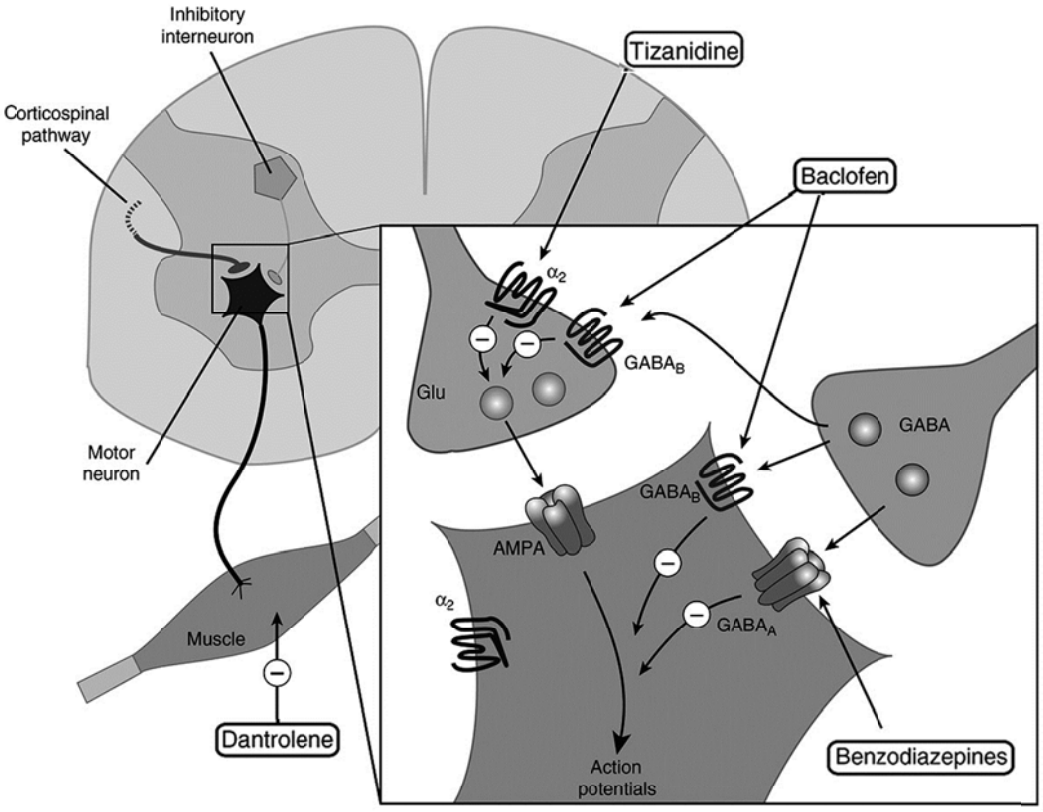
5. Chloral hydrate

- It is one of the oldest hypnotic drugs. It is an alcohol derivative.
- It produces hypnosis in 30 min and last for 6 hrs.
- It is used mainly as a hypnotic in children and elderly before short surgical or dental procedures but its use now is **very limited**.

Part 4: Skeletal Muscle Relaxants

Classification

- **Drugs act on brain higher centers:** e.g. carisoprodol, benzodiazepines, general anesthetics, anticonvulsant drugs, and antiparkinsonian drugs (see later).
- **Drugs act on neuronal transmission in the spinal cord:** e.g. tizanidine and baclofen.
- **Drugs act on the neuromuscular junction:** e.g. neuromuscular blockers and botolinum toxin.
- **Drugs act directly on the muscle contractile mechanisms:** e.g. dantrolene.



Sites of spasmolytic action of benzodiazepines (GABA-A), baclofen (GABA-B), tizanidine (α2) in the spinal cord and dantrolene (skeletal muscle). AMPA, amino-hydroxyl-methyl-isosoxaz-ole-proprionic acid, a ligand for a glutamate receptor subtype; Glu, glutamatergic neuron.

1. Carisoprodol

- Carisoprodol – (and its metabolite **mebrobamate**) – are centrally acting skeletal muscle relaxants. Their mechanism is unclear but seems to be similar to **barbiturates**. They bind to **$GABA_A$** receptors in the CNS leading to antianxiety, anticonvulsant, and skeletal muscle relaxation.
- The drug and its metabolite have **abuse** potential, so some countries limit its use.

2. Baclofen

- Baclofen is a GABA derivative that selectively stimulates **$GABA_B$** receptors in the spinal cord → ↓ release of excitatory transmitters.
- It is used as a skeletal muscle relaxant in neurological spastic conditions.

3. Tizanidine

- Tizanidine is a centrally acting **α2** agonist with greater effect on presynaptic α2 in the **spinal cord,** so it inhibits neurotransmission and reduces muscle spasm with minimal effect on blood pressure.

4. Dantrolene

- Dantrolene inhibits Ca^{2+} release from the sarcoplasmic reticulum of skeletal ms cells. It acts directly on the muscle contractile mechanisms.
- It is used for emergency management of **malignant hyperthermia** (1 mg/kg i.v.)

5. Botulinum toxin (Botox)

- Botulinum toxin is a neurotoxic protein produced by the bacterium *Clostridium botulinum*. It inhibits the release of ACh from motor nerve terminals leading to skeletal muscle paralysis.
- It is injected locally to treat local muscle spasm e.g. in cervical dystonia (spasmodic torticollis), and blepharospasm (uncontrolled muscle contraction or twitch of the eyelid). It is also used for cosmetic reduction of facial wrinkles.

6. Neuromuscular blockers: see ANS.

Therapeutic uses of skeletal muscle relaxants

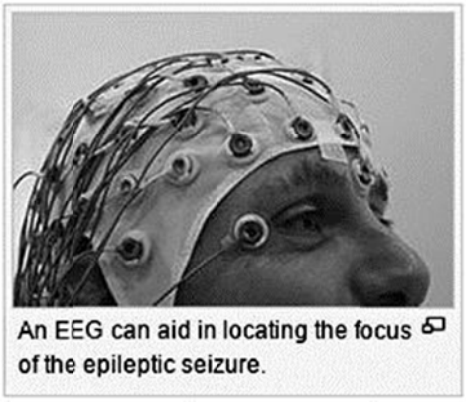
- Neurological spastic conditions such as multiple sclerosis, back pain, and spine injuries.
- Dantrolene is used for emergency management of malignant hyperthermia.
- Botolinum toxin is injected locally to relive blepharospasm, and for cosmetic reduction of facial wrinkles.
- Neuromuscular blockers are used to produce muscle relaxation during surgical procedures.

Mephensin

- Mephensin is a selective inhibitor of polysynaptic excitation of the spinal motor neurons through stimulation of **glycine receptors** in the spinal cord.
- It was historically used as antidote for treatment of **strychnine poisoning** but its clinical use now is **very limited** because of **serious side effects** including respiratory depression and hemolysis.

Part 5: Antiepileptic Drugs

Basic information


An EEG can aid in locating the focus of the epileptic seizure.

- **Epilepsy,** a chronic disease, occurs in approximately 1% of the population. The cause of most cases of epilepsy is unknown, although some people develop epilepsy as the result of brain injury, stroke, brain tumor, and drug toxicity. Genetic mutations are linked to a small proportion of the disease.
- Epileptic seizures result from excessive and abnormal cortical nerve cell activity in the brain.
- The diagnosis typically involves ruling out other conditions that cause similar neurological symptoms. This may be confirmed by brain imaging and electroencephalogram (EEG) but a normal test does not exclude the condition.
- Antiepileptic drugs (AEDs) are effective for about 80% of these patients. Lifelong treatment may be necessary.
- It may take weeks to establish adequate drug plasma levels and to determine the adequacy of therapeutic improvement. **Lack of compliance** is responsible for many treatment failures.
- AEDs are **most effective** and have the **least adverse effects** when they are used as **monotherapy.**
- Addition or withdrawal of any drug should be **gradual**, because seizures may occur on withdrawal.
- Some AEDs are **teratogenic;** this may call for the reduction or termination of therapy during pregnancy.

Classification of epilepsies:

Epilepsies are characterized by either focal or generalized abnormal neuronal discharges. Drug selection, based on seizure classification, is listed below in the order of general choice.

Partial seizures	**Simple partial**	Localized discharge; consciousness is not altered.	1. Carbamazepine 2. Lamotrigine 3. Valproic acid
	Complex partial	Localized discharge that becomes widespread; accompanied by loss of consciousness.	

Generalized seizures	**Tonic–clonic** (grand mal)	Dramatic convulsions with either jerking of the extremities or rigidity of the entire body; accompanied by loss of consciousness.	1. Valproic acid 2. Lamotrigine 3. Carbamazepine
	Absence (petit mal)	Sudden onset of altered consciousness that lasts 10–45 seconds, with up to hundreds of seizures per day; begins in **childhood** or adolescence.	1. Ethosuximide 2. Valproic acid 3. Clonazepam
	Myoclonic syndromes	Lightning-like jerks of one or more extremities occurring singly or in bursts of up to a hundred; accompanied by alteration of consciousness.	1. Valproic acid 2. Lamotrigine

- **Status epilepticus:**

  Prolonged seizure (>20 min) of any of the types previously described; the most common is life-threatening generalized tonic–clonic status epilepticus.

1. Diphenylhydantoin (Phenytoin)

Mechanism: it blocks Na^+, K^+ and Ca^{2+} channels in the **brain** (and **heart)** leading to decrease propagation of abnormal impulses. It produces some degree of drowsiness.

Any antiepileptic drug must have one or more of the **following mechanisms:**

1. **Decrease brain excitability** through blocking Na^+ or Ca^{2+} influx.
2. **Enhancement of GABA action.**
3. **Inhibition of excitatory transmitters** (aspartate and glutamate).

Therapeutic uses

- Partial and generalized seizures
- Status epilepticus: it should be given **i.v.** in the form of **fosphenytoin** (prodrug).
- Ventricular arrhythmia.

Adverse effects

– CNS: Nystagmus, diplopia, ataxia.
– Hepatotoxicity.
– Microsomal enzyme induction.
– Bone marrow depression & Megaloblastic anemia (due to ↓ folic acid).
– Teratogenicity: craniofacial abnormalities.
– Gingival hyperplasia: 2ry to increased expression of platelet derived growth factor (PDGF).
– Lymphadenopathy.

2. Carbmazepine (Tegretol)

Mechanism: it blocks Na^+ channels & ↓ excitability of cortical neurons.

Therapeutic uses

- Partial and generalized seizures (grand mal epilepsy).
- Trigeminal neuralgia.

Adverse effects

- CNS: diplopia & ataxia.
- Hepatotoxicity.
- Microsomal enzyme induction.
- Bone marrow depression.
- Congestive heart failure (CHF).

3. Valproic acid (Depakene)

Mechanism: it activates *glutamic acid decarboxylase* enzyme→ ↑ GABA synthesis.

Therapeutic uses: all types of epilepsy.

Adverse effects

- Sedation
- Microsomal enzyme inhibition
- Teratogenicity.
- Alopecia
- Pancreatitis

4. Ethosuximide (Zarontin)

Mechanism: blocks neuronal voltage-dependent Ca^{2+} and Na^+ channels.

Therapeutic uses: absence seizures (petit mal epilepsy) **(1st choice).**

Adverse effects

- Sedation
- Vomiting
- Leucopenia

5. Benzodiazepines: Clonazepam and diazepam

Mechanism: allosteric modulation of GABA action to facilitate its effects.

Therapeutic uses

- Clonazepam: petit mal epilepsy.
- Diazepam: status epilepticus.

Adverse effects: see before.

6. Barbiturates: Phenobarbitone

Mechanism: enhancement of GABA-mediated inhibition of glutamate excitation.

Therapeutic uses: grand mal epilepsy (contraindicated in petit mal epilepsy).

Adverse effects: see before.

NEWER ANTIEPILEPTIC DRUGS

1. Felbamate

Mechanism

- Block glycine site on the N-methyl-D-aspartate (NMDA) receptors.
- Block voltage-dependent Ca^{2+}& Na^{+} channels.

Therapeutic uses: wide variety of partial and generalized seizures.

Adverse effects

– Hepatotoxicity
– Microsomal enzyme induction.
– Bone marrow depression.

2. Lamotrigine

Mechanism

- Decreases glutamate and aspartate, which are excitatory neurotransmitters
- Blocks sodium channels and high voltage-dependent calcium channels leading to ↓ excitability.

Therapeutic uses: wide variety of partial and generalized seizures and typical absence seizures in children and adults.

3. Gabapentin

Mechanism: unknown but may interfere with voltage-dependent Ca^{2+} channels

Therapeutic uses: as adjuvant therapy in wide variety of partial and generalized seizures.

Adverse effects: headache, nystagmus, dizziness & ataxia.

4. Tiagabine

Potent and specific inhibitor of GABA uptake into glial and other neurons. Thus, it enhances the action of GABA by decreasing its removal from the synaptic space.

Precautions during antiepileptic therapy

- Proper **choice** of the antiepileptic drug according to type of epilepsy.
- Start with **single drug** and if fails, substitute it or add another drug.
- **Dose** of the drug is adjusted according to:
  - *Plasma concentration of the drug.*
  - *Patient's response.*
- Therapy is given for 2-3 years then withdrawn **gradually**.

Drugs used for treatment of Status epilepticus

Diazepam (drug of choice) 10 mg i.v. or 500 μg/kg **rectal** (in children) **OR:**

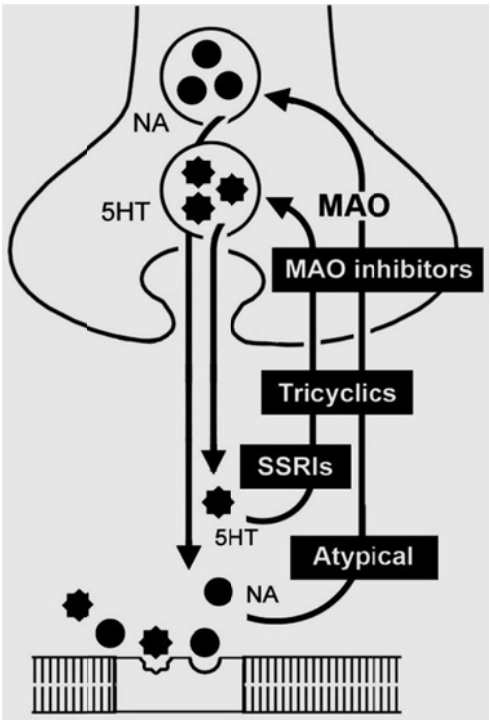
- Fosphenytoin: 100 mg i.v.
- Phenobarbitone: 200 mg i.v.
- In severe cases:
  a) Thiopental i.v.
  b) Artificial respiration.

Part 6: Antidepressant Drugs

Basic information

- Depression is a disorder of mood rather than disturbance of thought or cognition. It is postulated that depression is due to **deficiency** of **NA** and/or **5-HT** in the CNS while **mania** results from functional **excess**. Psychic depression is characterized by both ***emotional*** and ***biological*** symptoms.
- Recent studies suggest that overactivity of post-synaptic **5-HT$_2$A** receptors in some brain areas is involved in the pathogenesis of depression and psychosis.
- **Unipolar depression (major depressive disorder):** more common, may be ***reactive*** (70%) or ***endogenous*** (25%), characterized by low mood and loss of interest or pleasure in normally enjoyable activities.
- **Bipolar depression (manic-depressive disorder):** less common, characterized by oscillating periods of depression and mania. There is strong hereditary origin.
- The therapeutic effect occurs only after **2-3 weeks** of drug administration and is more closely associated with adaptive changes in neuronal receptors and brain neurotropic factors.

The sad woman by Edith Wilkinson



Classification of antidepressant drugs:

- **Tricyclic antidepressants (TCA)** e.g. imipramine, amitriptyline.
- **Selective serotonin reuptake inhibitors (SSRI):** e.g. fluoxetine, sertraline.
- **Atypical heterocyclic antidepressants:** e.g. maprotiline, trazodone.
- **Monoamine oxidase inhibitors (MAOI)** e.g. clorgyline, selegiline.

1. Tricyclic antidepressants (TCA)

Imipramine, Desipramine, Clomipramine, Amitriptyline, Nortriptyline

Pharmacokinetics

- They are well absorbed after oral administration. They have **large Vd**.
- Most TCA have **long $t_{1/2}$** because they are metabolized into active metabolites and undergo enterohepatic cycling.

Mechanism of action: *(inhibition of the amine pump)*

- TCA inhibit neuronal reuptake of both 5-HT & NA leading to their accumulation in synaptic spaces and the brain tissue.
- It has been suggested that improvement of the **emotional** symptoms is related to enhancement of **5-HT** transmission while improvement of **biological** symptoms is related to enhancement of **NA** transmission.
- Elevation of mood in depressed patients occurs after 2-3 weeks

Therapeutic uses

- Major depressive disorder.
- Nocturnal enuresis in children (**imipramine**).
- Chronic pain syndromes, neuropathic pain, and prophylaxis of migraine (unclear mechanism).

Adverse effects

- **Sedation** is common at the start of therapy but tolerance develops later. It may be due to antagonism with histamine H1 and/or muscarinic receptors.
- **CNS troubles:** memory dysfunction, agitation, seizures, and suicidal thoughts.
- **Atropine-like action:** very common - dry mouth, blurred vision, urine retention, etc.
- **Orthostatic (postural) hypotension**: due to peripheral **α1** receptor blockade.
- Cardiac **arrhythmias:** tachycardia, widening of QRS, and ↑ QT interval.
- **Hepatotoxicity:** cholestatic hepatitis.
- Weight gain.

Drug interactions

- Toxic synergism with **MAOIs** and **SSRIs** (irritability and convulsions).
- TCA antagonize the antihypertensive effect of **clonidine** and **methyldopa**.
- TCA have additive **anticholinergic effect** with other drugs having anticholinergic activity.

TCA overdose

- Metabolic acidosis
- Atropine-like effects
- Cardiac arrhythmia

Management

- IV NaHCO3 (1st step).
- IV lidocaine
- Dialysis is ineffective

2. Selective serotonin reuptake inhibitors (SSRIs)

Fluoxetine, Paroxetine, Sertraline, Citalopram, Escetalopram

- They are the most commonly prescribed antidepressants due to their limited toxicity. They are also used for some other psychiatric disorders.
- **Sertraline** is the preferred antidepressant following **myocardial infarction** as there is more evidence for its safe use in this situation than other antidepressants.
- When stopping an SSRI the dose should be **gradually** reduced over a 4 week period, this reduces the risk of relapse.

Mechanism of action

- They selectively block 5HT reuptake leading to accumulation of 5-HT in brain tissue.
- Their effect appears after 2-3 weeks like other antidepressants.

Therapeutic uses

- Major depressive disorder.
- Obsessive-compulsive disorder (OCD).
- Anxiety disorders (generalized anxiety disorder, social phobia, panic disorder).

Adverse effects

- **GIT irritation** is the most common side effect. A **proton pump inhibitor** should be prescribed if a patient is also taking a NSAID to avoid GIT bleeding.
- **Sedation** or **insomnia** at the start of therapy but tolerance develops later.
- **Muscle cramps** and twitches.
- **Sexual dysfunction** in up to 40% of patients – the main cause of noncompliance.
- Dangerous **"serotonin reaction"** may occur if given with **MAOIs** or **TCA** (hyperthermia, muscle rigidity, cardiovascular collapse).

3. Atypical antidepressants

The pharmacological properties of atypical heterocyclic antidepressant agents are similar to those of TCAs.

Mechanism of action

- **Trazodone:** blocks mainly **$5HT_2A$** receptors in addition to **H1**, and **α1** receptors. It is highly sedating and can cause postural hypotension.
- **Mertazapine:** blocks mainly **$5HT_2A$** receptors in addition to **H1**, and **α2** receptors. It causes weight gain.
- **Maprotiline:** selective blocker of **NA reuptake**. It is highly sedating and can cause seizures.

4. Monoamine oxidase inhibitors (MAOIs)

Clorgyline, Selegiline, Pargyline, Moclobemide

Mechanism of action

- They inhibit MAO enzyme leading to accumulation of active monoamines (NA, 5-HT, dopamine) in neuronal tissue.
- Most MAOIs are **irreversible inhibitors**. Recovery of MAO takes several weeks. **Moclobemide** is a **reversible** inhibitor.

N.B. There are 2 isotypes of MAO enzyme:

MAO-A enzyme
- Present in the cytoplasm of neurons (CNS) and peripheral tissues (e.g. liver).
- It acts non-specifically on NA, 5-HT, and dopamine.
- **Clorgyline** is a specific inhibitor.

MAO-B enzyme
- Present mainly in the CNS and acts more on dopamine.
- **Selegiline** is a specific inhibitor.

Therapeutic uses

- **Major depression:** they are **not** used as a first-line, but usually reserved as a last line after other classes of drugs have failed.
- **Selegiline** (selective MAO-B inhibitor) is used for treatment of **Parkinsonism** (see later).

Adverse effects

- **CNS stimulation:** irritability, insomnia, tremors, hyperthermia, convulsions
- **Hepatotoxicity**: occurs more with the old members.
- **Orthostatic (postural) hypotension** and **sexual dysfunction**.

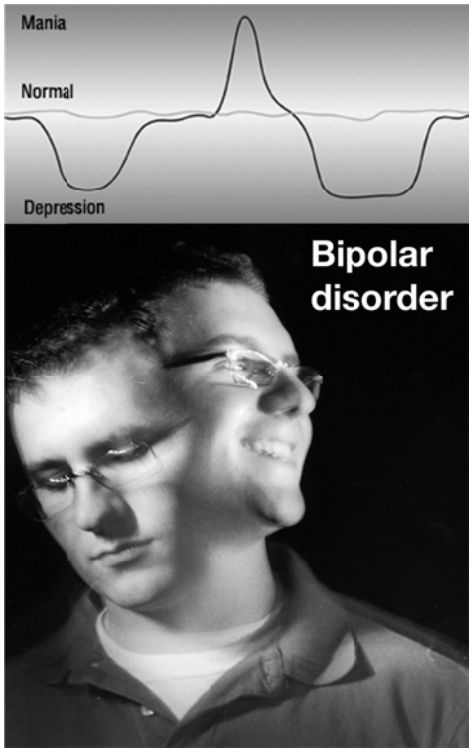
Interactions

- **Drug-drug interactions:**
  - Toxic synergism with **tricyclic antidepressants** and **SSRIs**.
  - Potentiation of **sympathomimetics** (including cold remedies & nasal decongestants).

- **Drug-food interactions: Hypertensive crisis (cheese reaction):**
  - **Tyramine** is an indirect sympathomimetic present in some food and normally metabolized by MAO-A in the liver.
  - When the patient takes MAO-A inhibitor or non-selective MAOIs, severe hypertension can occur after eating tyramine-rich food *e.g. fermented cheese, yogurt, beer, herrings*.
  - Treatment: by giving combined α + β blockers (prazosin + propranolol).

Part 7: Mood Stabilizing Drugs (treatment of mania and bipolar disorder)

- **Sodium valproate** is the only specific antimanic agent and is the treatment of choice in the **acute stages**.
- **Lithium** is the drug of choice for **long-term** treatment to prevent relapse.



Lithium carbonate

Mechanism of action

- It ↓ cAMP in neuronal cells and ↓ NA release → ↓ neuronal firing.
- It inhibits many metabolic processes in the nerve tissue.

Therapeutic uses

- Treatment of **mania** *(valproate is the 1st choice).*
- Treatment of **manic-depressive disorder** (bipolar depression)**.** It is given in the manic phase while TCA or SSRIs are given in the depressive phase.

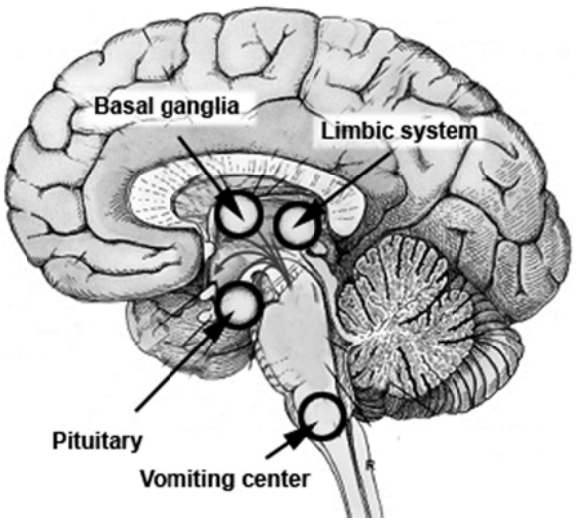
Adverse effects

- Lithium has a very narrow therapeutic index, monitoring of plasma levels is essential.
- It has long plasma half-life being excreted entirely by the kidneys.
- Toxicity may be precipitated by dehydration, renal failure, diuretics (especially thiazide) or ACE inhibitors.

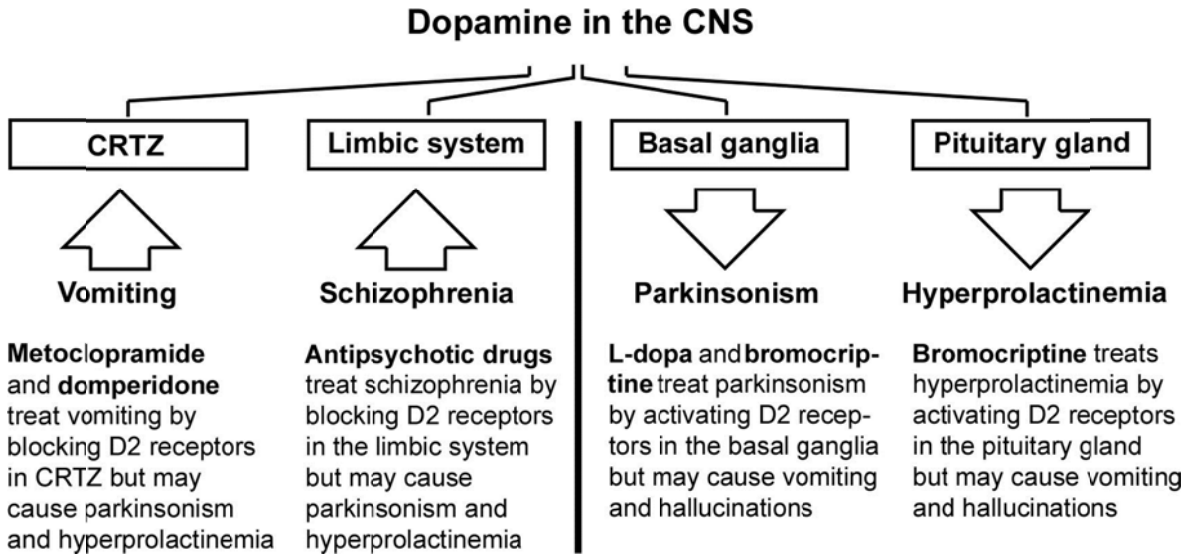
– Anorexia, nausea, vomiting and diarrhea.
– Nephrogenic **diabetes insipidus** leading to polyurea and thirst.
– Hypotension and cardiac **arrhythmia**.
– **Thyroid** dysfunction
– **Fine tremors** (coarse tremors are seen with toxic levels).
– Teratogenicity.

Part 8: Antipsychotic Drugs (Neuroleptics)

Basic information



Central dopaminergic pathways and drugs affecting them:


Dopamine in the CNS
CRTZ
Limbic system
Basal ganglia
Pituitary gland
Vomiting
Schizophrenia
Parkinsonism
Hyperprolactinemia
Metoclopramide and domperidone treat vomiting by blocking D2 receptors in CRTZ but may cause parkinsonism and hyperprolactinemia
Antipsychotic drugs treat schizophrenia by blocking D2 receptors in the limbic system but may cause parkinsonism and hyperprolactinemia
L-dopa and bromocriptine treat parkinsonism by activating D2 receptors in the basal ganglia but may cause vomiting and hallucinations
Bromocriptine treats hyperprolactinemia by activating D2 receptors in the pituitary gland but may cause vomiting and hallucinations

- The term "**psychosis**" denotes a variety of mental disorders. **Schizophrenia** is a particular kind of psychosis characterized by abnormal social behavior and failure to recognize what is real.
- Common **"positive"** symptoms include false beliefs (delusions), unclear or confused thinking, and auditory hallucinations. **"Negative"** symptoms include reduced social engagement, blunted emotions, and inactivity.
- It is suggested that **central dopamine overactivity and $5HT_2A$ receptors** play important role in the pathogenesis.

Self-portrait of a person with schizophrenia, representing that individual's perception of the distorted experience of reality in the disorder

Classification of drugs

- **Typical (classic; old) neuroleptics:**
  - **Phenothiazines:** chlorpromazine, promethazine.
  - **Butyrophenones:** haloperidol, droperidol.
  - **Thioxanthenes:** thiothixene, chlorprothixene.

- **Atypical (newer) neuroleptics:**
  - **Risperidone– Olanzapine – Clozapine**

Mechanism and therapeutic action

- The **typical antipsychotic** drugs primarily block central **D_2** receptors in the mesolimbic and mesocortical areas of the CNS leading to ↓ hallucinations and delusions but can lead to serious **extrapyramidal** adverse effects.
- The **atypical antipsychotic** drugs combine between blockade of **D_2** (to a lesser degree) and **5-HT_2A** receptors, so they have **fewer extrapyramidal** side effects.
- The **typical antipsychotic** drugs have greater effect on the control of **positive** symptoms (hallucinations and thought disturbances), while **atypical** drugs have greater effect on **negative** symptoms (social withdrawal).

Therapeutic uses

- **Schizophrenia & mania (typical and atypical antipsychotics):**

– Antipsychotic drugs produce an **immediate quieting action.** However, their antipsychotic effects typically take **longer** time to occur (a week or more).

- **Other therapeutic uses of typical antipsychotics:**

– **Chloropromazine** is sometimes used to relieve **intractable hiccough** and as anaesthetic adjuvant in certain operations to produce **hypothermia.**

– **Severe nausea or vomiting** associated with, e.g., radiation treatment and cancer chemotherapy. Typical antipsychotic agents have strong antiemetic activity due to D2-receptor blockade in the chemoreceptor trigger zone (CTZ) of the medulla. The most commonly used are the phenothiazines **chloropromazine** and **promethazine**

Adverse effects

- **CNS:**
  - **Extrapyramidal manifestations:**
    – These adverse effects are related to a **D2-receptor blockade** in the basal ganglia. They occur most likely with **old** generation drugs.

- They include:
  - Parkinsonian-like syndrome
  - Dystonia: sustained muscle contractions cause twisting movements or abnormal postures
  - Dyskinesia: involuntary repetitive facial, lip, and tongue movements occurs with chronic therapy. It may be irreversible.

Dystonia caused by antipsychotic drugs.

- **Neuroleptic malignant syndrome:**
  - It is a serious complication with mortality rate 20%, occurs more with old generation drugs.
  - It consists of autonomic disturbance, ms rigidity, hyperthermia, and sweating.
  - It needs immediate stopping of the antipsychotic therapy.

- **Autonomic side effects:**
  - **α-receptor blockade** leading to postural hypotension and sexual dysfunction
  - **Muscarinic blockade** → atropine-like actions

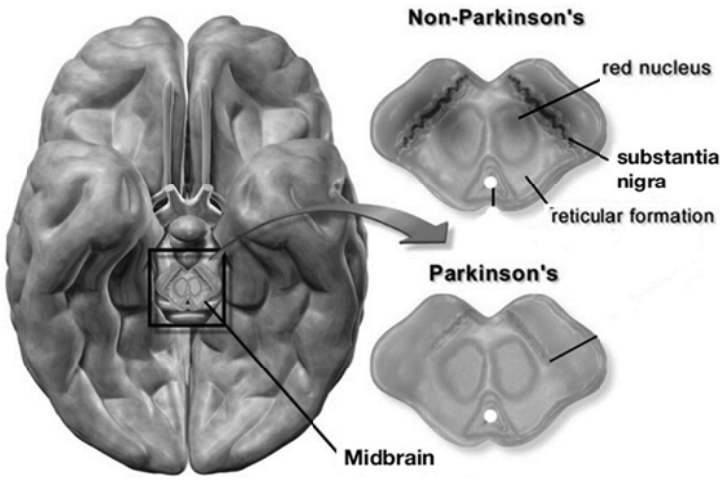
- **Endocrine disturbance (occurs more with atypical agents):**
  - Weight gain
  - Hyperglycemia and precipitation of DM.
  - Gynecomastia, amenorrhoea

- **Other adverse effects:**
  - Cardiac arrhythmia
  - Cholestatic jaundice
  - Agranulocytosis (particularly associated with **clozapine**)

	Typical drugs	Atypical drugs
Mechanism	Block mainly D2 receptors	Block D2 (less) and $5HT_2A$ (more)
Effect	More effect on +ve symptoms	More effect on – ve symptoms
Extrapyramidal side effects	Common	Less common
Neuroleptic malignant synd	Common	Less common
Endocrinal side effects	Less common	Common
Agranulocytosis	Less common	Common

Part 9: Antiparkinsonian Drugs

Parkinsonism is a movement disorder characterized by ms rigidity, tremors, and postural instability due to loss of **dopaminergic neurons in substantia nigra and locus ceruleus** resulting in imbalance of dopaminergic (inhibitory) and cholinergic (excitatory) influences on the extrapyramidal system. Recently, a heroin substitute (MPTP) was found to cause irreversible damage of the negrostriatal dopaminergic neurons and a parkinsonism-like state.



Diminished dopaminergic neurons in substantia nigra seen in Parkinsons disease

Classification of antiparkinsonian drugs:

- **Dopaminergic drugs:**
  - **Dopamine precursors:** Levodopa (L-dopa).
  - **COMT inhibitors:** Tolcapone - Entacapone
  - **Selective MAO-B inhibitors:** Selegiline
  - **Dopamine agonists:** Bromocriptine
  - **Release of dopamine** and inhibition of its reuptake: Amantadine
- **Antichloinergic drugs:**
  - **Synthetic atropine substitutes:** Benztropine – Orphenadrine – Trihexyphenidyl

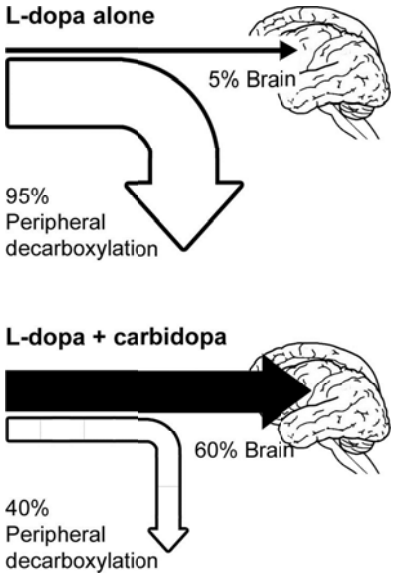
1. Levodopa (L-dopa)

Pharmacokinetics

- Absorbed rapidly from the small intestine.
- It has **short $t_{1/2}$** (1-2 h). This short $t_{1/2}$ may produce "*on-off phenomenon*" i.e. rapid fluctuation of the clinical state in the form of sudden tremors & immobility after short period of recovery.
- **Amino acids** (e.g. leucine & isoleucine) compete with L-dopa absorption from the gut so it should be taken on an empty stomach.

Mechanism of action

- Dopamine can't cross BBB but L-dopa can. It is considered the **1st line** treatment of parkinsonism.
- More than 95% of the administered dose is rapidly decarboxylated into dopamine in the peripheral tissues. Only a small fraction escapes and crosses BBB.
- Peripheral decarboxylation can be minimized by administration of a decarboxylase inhibitor which can't cross BBB e.g. **carbidopa** or **benserazide.**
- Such a combination helps to reduce the dose of L-dopa and hence the adverse effects



Adverse effects

- **GIT:** nausea & vomiting *(domperidone is the drug of choice to treat this vomiting because it does not cross the BBB. It acts on the bare area of the barrier).*
- **CNS:**
  - Mood changes, hallucinations and nightmares.
  - Dyskinesia: involuntary movements of the head, lips, and tongue.
  - On-off phenomenon: rapid fluctuation of the clinical state in the form of sudden tremors and immobility after a short period of recovery due to the short $t_{1/2}$ of the drug.
- **Autonomic:** postural hypotension, arrhythmias, mydriasis and acute rise of IOP.
- **Brownish** body secretions & red urine due to the metabolite *homovanilic acid.*

Interactions

- **Food:** amino acids (e.g. leucine & isoleucine) compete with L-dopa absorption**.**
- **Dopamine blockers** (antipsychotic drugs and metoclopramide) antagonize the effects of L-dopa.
- **Pyridoxine** (vitamin B6) enhances peripheral decarboxylation into dopamine.
- **COMT inhibitors** and **selective MAO-B inhibitors:** make synergism with L-dopa.

2. COMT inhibitors (L-Dopa adjuvants): Tolcapone - Entacapone

Mechanism of action

- They inhibit COMT enzyme selectively & reversibly, the enzyme that converts L-dopa to 3-O-methyldopa (3OMD) in the gut and liver.

- By inhibiting COMT enzyme, tolcapone increases the efficacy of L-dopa and stabilizes dopamine levels in the striatum and improves motor function.

Adverse effects

- Same side effects of L-dopa (nausea, vomiting, hallucination, mood changes).
- Tolcapone causes fulminating hepatic necrosis.

3. Selective MAO-B inhibitors: Selegiline

Mechanism of action

- It is a selective MAO-B inhibitor **decreasing breakdown** of dopamine in the brain.
- Unlike MAO-A inhibitors, it does not precipitate **"cheese reaction"** since tyramine is metabolized in the liver by MAO-A.

Adverse effects

- Nausea, vomiting & GIT upset.
- Hallucinations & mood changes.
- Insomnia.

4. Dopamine agonists: Bromocriptine

- It is dopamine (D_2) agonist derived from ergot alkaloids.
- It differs from L-dopa in: **Faster** onset, **longer** duration, **No** on-off effect.

Other uses

- To treat hyperprolactinemia and to suppress lactation (dopamine agonists ↓ prolactin secretion from pituitary gland).
- Acromegaly (dopamine agonists ↓ GH secretion from pituitary gland).

Adverse effects

- Nausea, vomiting & GIT upset.
- Hallucinations & mood changes in large doses.
- Postural hypotension.

5. Dopamine release stimulation: Amantadine

- It is an antiviral drug for influenza A2 virus.
- The antiparkinsonian mechanism is unclear but may be due to ↑ dopamine release, ↓ dopamine reuptake, or direct action on dopamine receptors.

Adverse effects

- Nausea, vomiting & GIT upset.
- Hallucinations & mood changes in large doses.
- Postural hypotension.
- Skin pigmentation.

Skin pigmentation "levido reticularis" caused by amantadine.

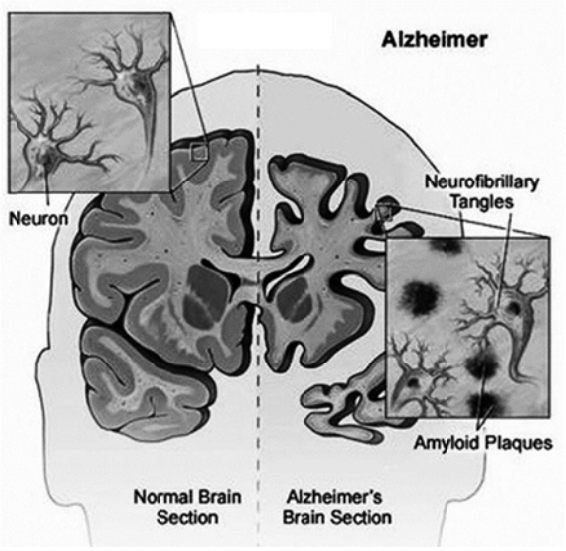
6. Anticholinergic drugs:

Benztropine – Orphenadrine – Trihexyphenidyl

- These drugs have **greater selectivity** for blocking central than peripheral muscarinic receptors.
- They produce moderate improvement of tremors and **sialorrhea** but little effect on muscle rigidity.
- They are used also to control acute drug-induced extrapyramidal side effects.
- These drugs are **contraindicated** in patients with **prostatic** hypertrophy, obstructive GI disease (e.g., paralytic ileus) and narrow-angle **glaucoma**.
- In patients suffering from Parkinsonism, there is some degree of **dementia** associated with atrophy of cortical neurons. Anticholinergic drugs may aggravate dementia and memory loss.

Part 10: Drugs Used in Alzheimer's Disease

Alzheimer is a neurodegenerative disease characterized by progressive loss of memory and dementia due to **loss of cholinergic neurons** and deposition of abnormal protein "amyloid plaques". Overstimulation of **glutamate receptors** may be responsible for this neurodegenerative process.



The aim of therapy is to either improving cholinergic transmission within the CNS or preventing the excitatory actions of NMDA glutamate receptors in selected brain areas.

1. Cholinesterase inhibitors: Donepezil - Rivastigmine

- They are more selective for ChE enzyme in the CNS
- They provide a modest reduction in the rate of loss of cognitive functions.
- **Side effects:** nausea, vomiting, anorexia, and muscle cramps.

2. NMDA receptor antagonist: Memantine

- It is a derivative of amantadine
- It prevents rate of memory loss in both vascular-associated and Alzheimer dementia.
- **Side effects are rare:** confusion, agitation, restlessness.

3. Recent trials:

- **β & γ-secretase inhibitors:**
  The enzymes β & γ-secretase are responsible for formation of amyloid proteins Aβ40 and Aβ42 that are found in the brain of Alzheimer patients. Inhibition of these enzymes reduces deposition of theses amyloid deposits.
- **Ibuprofen and indomethacin**
  These NSAIDs reduce formation of Aβ42 by inhibition of γ-secretase enzyme which is unrelated to their COX inhibition. Aspirin and corticosteroids do not produce this effect.
- **Copper and zinc chelating agents:**
  Removal of these metals promotes dissolution of amyloid plaques in brain tissue.

Part 11: General Anesthetics

General anesthesia is characterized by a loss of consciousness, analgesia, amnesia, skeletal ms relaxation, and inhibition of autonomic and sensory reflexes.

Balanced anesthesia

- Balanced anesthesia refers to a combination of drugs used to take advantage of individual drug properties and minimizing their adverse actions.
- In addition to anesthetic drugs and neuromuscular blocking drugs, other drugs are administered preoperatively, intraoperatively, and postoperatively to ensure smooth induction, sedation, and smooth recovery (e.g., benzodiazepines, opioids).

Stages and planes of anesthesia

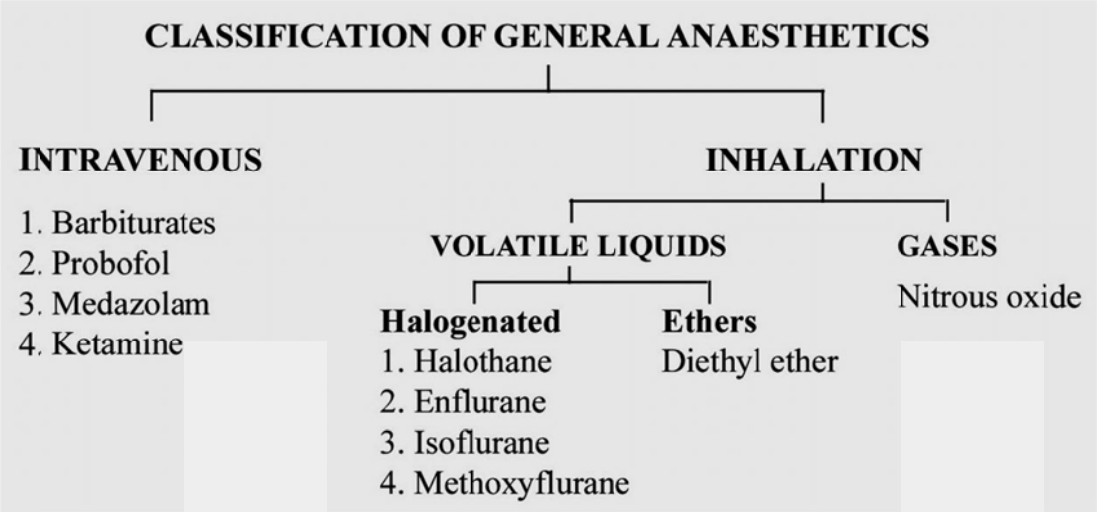
- The stages and planes of anesthesia identify the progression of physical signs that indicate the depth of anesthesia. Newer, more potent agents progress through these stages rapidly, and therefore, the stages are often obscured.
- Mechanical ventilation and the use of adjunct drugs also obscure the signs indicating the depth of anesthesia.
  - **Stage I:** Analgesia and amnesia.
  - **Stage II:** Excitation.
  - **Stage III:** Surgical anesthesia: loss of consciousness.
    - Four planes have been described relating to increased depth of anesthesia.
    - Plane IV includes maximal pupil dilation, apnea, and circulatory depression.
    - The loss of the eyelash reflex and a pattern of respiration that is regular in rate and depth are the most reliable signs of stage III anesthesia.
  - **Stage IV:** Medullary depression: respiratory and cardiovascular failure.

Mechanism of anesthetic action

Inhalation and IV anesthetic agent interaction with **discrete protein binding sites in nerve endings to activate ligand-gated ion channels:**

- **GABA-A-receptor chloride channels:** anesthetic agents directly and indirectly facilitate a GABA-mediated increase in chloride conductance to hyperpolarize and inhibit neuronal membrane activity.
- **Ligand-gated potassium channels:** anesthetic agents increase potassium conductance to hyperpolarize and inhibit neuronal membrane activity.
- **NMDA receptors:** certain anesthetics (e.g., nitrous oxide, ketamine) inhibit excitatory glutamate gated ion channels.

Classification of general anesthetics



INTRAVENOUS ANAESTHETICS

1. Ultrashort acting barbiturates: thiopental

Advantages

- Produces rapid and pleasant induction with rapid recovery.
- Does not increase intracranial pressure.
- Used for induction before stronger anesthetic and for short procedures.

Disadvantages

- Poor analgesia and skeletal muscle relaxation.
- Induce cough, laryngospasm, bronchospasm and apnea avoided by atropine and ready artificial respiration.
- Extravasation induces necrosis.
- Contraindicated absolutely in cases of prophyria (defect of ALA synthetase) barbiturates increase synthesis of porphyrins which precipitates acute attack inducing paralysis and death.

2. Etomidate

Advantages: It is very similar to thiopental but:

- Larger margin between the anaesthetic dose and the dose producing respiratory and cardiovascular depression than with thiopental.
- It is more rapidly metabolized than thiopental and, therefore, less likely to cause a prolonged hangover.
- It is used only as an induction agent, and is preferable to thiopental in patients at risk of circulatory failure.

Disadvantages

- More likely to cause involuntary movements during induction.
- And to cause postoperative nausea and vomiting.
- Suppresses the adrenal cortex with prolonged use which has been associated with an increase in mortality in severely ill patients.

3. Propofol

Advantages

- Rapid and pleasant induction with rapid recovery and clarity of mental status.
- Does not increase intracranial pressure.
- Used for induction or maintenance.

Disadvantages

- Respiratory center depressant less than thiopental.
- Markedly decreases the blood pressure.

4. Midazolam (see under Benzodiazepines)

- They are used in conjunction with anaesthetics to sedate the patient.
- The most commonly employed is midazolam.
- Diazepam and lorazepam are alternatives. All three facilitate amnesia while causing sedation.

Advantages

- Used for induction
- 3-4 times as potent as diazepam.
- Does not cause local irritation after injection as diazepam.
- Little cardiovascular or respiratory depression.

Disadvantages

- Light anaesthesia.
- Can cause respiratory depression.
- Anterograde amnesia which lasts for at least 2 hours.

5. Ketamine (Dissociative Anaesthesia)

Advantages

- Profound analgesia and amnesia
- The only intravenous anesthetic that routinely produces cardiovascular stimulation through central sympathetic stimulation (increases Bl.P. H.R and C.O.). So, it is beneficial in cases of shock.
- No respiratory depression and has a potent bronchodilator effects.

Disadvantages

- Increases intracraneal pressure (due to increased cerebral blood flow).
- Unpleasant dreams.
- Recovery often is accompanied by delirium and psychomotor activity).
- Diplopia and nystagmus may occur due to increased muscle tone.
- Contraindicated in cases of hypertension and stroke.

INHALATION ANAESTHETICS

An important characteristic of an inhalation anaesthetic is the speed at which the arterial blood concentration, which governs the pharmacological effect, follows changes in the concentration of the drug in the inspired air.

Measure of potency

- Through the minimum alveolar concentration (MAC). It is the anaesthetic (MAC) alveolar concentration at 1 atmosphere that will produce loss of movement in 50% of subjects exposed to a noxious stimulus.
- Methoxyflurane is highly potent while nitrous oxide is of low potency.

Rapidity of induction

- Gas of little solubility in blood as nitrous oxide has a high blood gas tension, a small Vd, with a consequent rapid induction and rapid recovery.
- Gas of high solubility in blood e.g. methoxyflurane has a low blood gas tension, a big Vd, with a slow induction and a slow recovery.

Pharmacological effects

- Inhalation anaesthetics produce descending depression of all brain functions in the following order: Cortex >Subcortex> Mid-brain > Spinal cord > Medullary centers.
- The highly developed functions like memory are the first to be lost, but the vital functions as respiration and circulation are the last.
- With modern balanced anaesthesia no more notable staging. Loss of consiousness, analgesia and muscle relaxation is produced with a combination of drugs rather than with a single anaesthetic agent.
- Unconsciousness rapidly produced with an i.v. induction agent (e.g. propofol), to maintain unconsciousness and produce analgesia with one or more inhalation agent which might be supplemented with an i.v. analgesic agent, and to produce muscle paralysis with a neuromuscular blocking drug.
- The following table shows points of difference in between the currently used inhalation anesthetics:

Inhalation anesthetics

	Ether	Nitrous Oxide	Halothane	Enflurane	Methoxy Flurane
1- MAC	1.9	> 100 (the least potent)	0.75	1.7	0.16 (the most potent)
2- Induction and recovery	rapid	rapid	Slow	slow	slow
3- Analgesia	good	good	Inadequate	potent	potent (continues after recovery)
4- Skeletal muscle relaxation	good	not relaxant	Inadequate	good	good
5- C.V.S	--------	--------	Bradycardia, arrhythmias and hypotension	less than halothane	less than halothane
6- Respiration	Bronchodilataion by the sympathetic stimulation	Diffusion hypoxia at the termination	Respiratory center depression	- more respiratory center depression - Inhibits bronchoconstriction	more
7- Liver	Increased glycogenolysis by the sympathetic stimulation	-----	autoimmune hepatitis	less than halothane (rare)	less than halothane (rare)
8- Uterus	----------	No uterine relaxation	potent uterine relaxant	less uterine relaxation	No uterine relaxation
9- Hyperthermia	----------	-------	rare	rare	rare
10- Use	* Suitable for most types of operations * Of wide safety margin	* The most widely used * Obstetric anesthesia . * Neuroleptanaesthesia	- Safe for children and for asthmatics	lower incidence of arrthythmias than halothane	* Limited use because of nephrotoxicity * Obsetetric anaesthetic.
11- Disadvantages	* Inflamable * Irritant * Precipitaes convulsions	* Weak anaesthetic * Has no skeletal muscle relaxant effect * Diffusion hypoxia	* Hepatitis * Malignant hyperthermia * Contraindicated in cardiac	* Nephrotoxic * EEG. seizure activity (contraindicated in epileptics)	Nephrotoxic (damage of tubules by the liberated fluoride diabetes insipidus induced by fluoride)

Preanesthetic medications (anesthetic adjuvant):

They are drugs given to reduce anxiety, providing analgesia and amnesia, and prevent salivation, bradycardia, and other side effects of anesthesia.

- **Anxiolytics (e.g. diazepam):** given at night preoperatively to provide sedation & amnesia.

- **Opioid analgesics (e.g. morphine, fentanyl, or alfentanil):**
  - They are given 1½ hrs before anesthesia to inforce low potency anesthetics as nitrous oxide.Alfentanyl may offer faster recovery than fentanyl.

- **Anticholinergic drugs (e.g. atropine or scopolamine):**
  - They are given 1½ hrs before anesthesia to reduce respiratory secretions and prevent occurrence of aspiration pneumonia.
  - They block the reflex vagal stimulation induced by some inhalation anesthetics.

- **Muscle relaxants & others drugs:** e.g. **vasopressors** to prevent hypotension and **hypothermics** (chlorpromazine) to lower the normal body temperature in cases of cardiac surgery.

Part 12: Local Anesthetics

Classification

There are two classes of local anesthetics: **amides** and **esters**. The primary differences between the two classes are in their relative metabolism (amides have primarily a hepatic metabolism, whereas esters are metabolized by plasma cholinesterases) and their potential for allergic reactions (esters more than amides).

	Esters	Amides
Members	Cocaine, procaine, tetracaine, benzocaine	Lidocaine, prilocaine, mepivacaine, bupivacaine
Metabolism	Plasma cholineestrase	Liver
Hypersensitivity reactions	May occur	Rare

Mechanism of action

- Local anesthetics block voltage dependent Na^+ channels within the nerve fibers →↓ nerve conduction.
- In general, small nerve fibers (that carry pain sensation) are more sensitive to local anesthetics than large fibers (motor and other sensations).
- Myelinated fibers are blocked before non-myelinated fibers of the same diameter.

Pharmacological properties

	Chemistry	Anesthetic potency	Duration	Onset
Procaine	Ester	Low	Short	Moderate
Mepivacaine	Amide	Moderate	Moderate	Fast
Prilocaine	Amide	Moderate	Moderate	Fast
Lidocaine	Amide	Moderate	Moderate	Fast
Tetracaine	Ester	High	Long	Moderate

Adjuvants of local anesthetics

- **Vasoconstricotors e.g. adrenaline:**
  - They are added to produce local VC; this will reduce wash of the anesthetic by the local blood flow and thus prolongs the duration of the anesthetic.

- Vasoconstrictors should not be added for ring block of hands, feet, fingers, toes, and ear pinna to avoid tissue damage.

- **Sodium bicarbonate:**
  - All local anesthetics are weak **bases**. Addition of bicarbonate to the anesthetic solution maintains the anesthetic in the non-ionized state and this increases lipid solubility and enhances penetration of the anesthetic into the nerve sheath.

Techniques and clinical uses

- **Surface (topical) anesthesia:** is used for anesthetization of the skin, mucous membranes, or cornea.
  - Treatment of itching caused by insect bites or irritant condition.
  - To relieve pain caused by oral, laryngeal, or rectal disorders e.g. piles.
  - Corneal anesthesia in ophthalmic surgery.

- **Infiltration anesthesia:** injecting an anesthetic directly into the subcutaneous tissue for minor surgical procedures e.g. dental procedures. Epinephrine may be added to prolong the duration of action.

- **Nerve block:** injecting the local anesthetic close to the appropriate nerve trunk proximal to the intended area of anesthesia e.g. radial nerve block or retro-orbital block for ocular surgery.

- **Spinal anesthesia:** is used for surgeries of the lower limb or pelvic structures. A local anesthetic is injected into the subarachnoid space below the terminal end of the spinal cord (usually between 3rd and 4th lumber vertebra).

- **Epidural anesthesia:** the anesthetic is infused into the space between the dura mater and the connective tissue lining the vertebral canal as alternative to subarachnoid anesthesia.

Adverse effects

- **Surface anesthesia:** allergic dermatitis.

- **Infiltration anesthesia:** faulty intravascular injection can lead to:
  - CNS excitation: irritability and convulsions
  - CVS depression: bradycardia, hypotension, myocardial depression or cardiac arrest.

- **Vasovagal syncope**: vasovagal (also called neurocardiogenic) syncope is usually associated with bradycardia (rather than tachycardia) and pallor (rather

than flushing). These differences can be helpful in distinguishing it from anaphylaxis.

– **Spinal anesthesia:**
  - Spinal shock due to sympathetic outflow paralysis.
  - Headache due to CSF leakage.
  - Respiratory paralysis.
  - Septic meningitis.

Recommendations

- The **choice** of local anesthetic for infiltration depends on several factors, including duration of the procedure, need for hemostasis, patient sensitivity to catecholamines, and patient allergy to local anesthetics.
- Prior to infiltration, the clinician should determine if the patient has any **history of allergy.** Patients with a true allergic reaction to a local anesthetic need evaluation by an allergy specialist.
- Local anesthetic infiltration is **contraindicated** in the following conditions:
  – If the area needed to be anesthetized is so large because the amount of anesthetic needed exceeds the maximal safe dose.
  – If the patient has history of allergy to local anesthesia.

Treatment of spinal shock

- **Place the patient in the supine position with the legs elevated.**
- **Airway support:** oxygen and artificial respiration.
- **If there are convulsions, give i.v. diazepam.**
- **If there is hypotension**, give i.v. fluids plus vasoconstrictors.
- Cardiopulmonary resuscitation (CPR) is necessary when cardiac function is interrupted.

Notes

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Pharmacology
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Review Questions

Long questions:

1. Classify **opioid analgesics** and discuss mechanism, uses, &contraindications of morphine.
2. Anxiety is a common medical disorder. Classify **antianxiety drugs** and discuss in details the differences between barbiturates and benzodiazepines.
3. **Depression is an important medical disease. Classify** antidepressant drugs; **mention their mechanism, indications and side effects.**
4. Classify **antiepileptic drugs**; mention their mechanism, indications and side effects.
5. **Dopamine** is found in many areas in the CNS. Discuss the drugs that act by inhibiting these central dopamine sites.
6. **Dopamine** is found in many areas in the CNS. Discuss the drugs that act by activating these central dopamine sites.

Short questions:

1. **Give an account on:**
   a) Mechanism and treatment of paracetamol toxicity
   b) Drug treatment of Alzheimer's disease.

2. **Discuss the pharmacodynamic principles underlying the use of:**
   a) Morphine in acute pulmonary edema.
   b) Acetylcysteine in paracetamol toxicity
   c) Naloxone in acute opioid toxicity.
   d) Selegiline in parkinsonism.

3. **Discuss on pharmacological basis of each of the following:**
   a) Nalorphine is contraindicated to relive pain in addict patient.
   b) Reserpine is contraindicated with MAOIs.
   c) Anticholinergic drugs are not preferred to treat parkinsonism in old patients.

4. **Mention drug interactions of each of the following drugs:**
   (1) L-Dopa (2) MAOIs

5. **Mention the main differences between:**
   a) Valproic acid and lamotrigine
   b) L-Dopa and bromocriptine.
   c) Chloropromazine and olanzapine

Of each of the following questions, select ONE BEST answer:

1. Morphine, all are true EXCEPT:
A. Acts as an agonist at opioid receptors (especially μ) in the brain and spinal cord
B. Causes pupillary constriction by stimulation of the Edinger–Westphal nucleus in the mid-brain
C. Acts as an antihistamine
D. Is subject to presystemic metabolism
E. Stimulates the chemoreceptor trigger zone

2. Which of the following is not true for meperidine?
A. It has less analgesic potency than morphine
B. It has less spasmogenic effect than morphine
C. It can cause histamine release and bronchoconstriction
D. It has greater bioavailability than morphine
E. It does not cause physical dependence

3. Morphine causes all of the following EXCEPT:
A. Diarrhoea
B. Increased intrabiliary pressure
C. Histamine release
D. Reduced sensitivity of the respiratory centre to carbon dioxide
E. Hypotension

4. The following are particularly sensitive to the pharmacological actions of morphine EXCEPT:
A. Young children
B. The elderly
C. Patients with hepatic failure
D. Patients with renal failure
E. Patients with hyperthyroidism

5. The pharmacologic effects of acetylsalicylic acid include:
A. Reduction of high body temperature
B. Promotion of platelet aggregation
C. Reduction of pain by stimulation of PGs synthesis
D. Efficacy equals to that of probenecid as uricosuric agent
E. Less gastric irritation than other NSAIDs

6. Aspirin reduces the synthesis of the following eicosanoids EXCEPT:
A. TXA2
B. PGE2
C. PGF2α
D. LTB4
E. PGI2

7. The following statements about NSAIDs are correct EXCEPT:
A. Diclofenac may cause permanent platelet dysfunction
B. Indomethacin may cause neurological side effects (neurotoxicity).
C. Sulindac is a prodrug
D. They may impair renal function
E. Aspirin may displace coumarin anticoagulants from plasma proteins

8. The following statements about aspirin are correct EXCEPT:
A. May cause GIT hemorrhage after a single dose
B. Enteric-coated tablets cause less gastric bleeding
C. May cause metabolic alkalosis in high doses
D. May cause Rye's syndrome in children
E. Its toxicity may require treatment with hemodialysis

9. Which one of the following statements concerning Cox-2 inhibitors is correct:
A. They show greater analgesic activity than traditional NSAIDs
B. They show anti-inflammatory activity greater than traditional NSAIDs
C. They harm the stomach as do non-selective cox inhibitors
D. They increase platelet aggregation
E. They are cardio protective

10. Non-narcotic analgesics are all of the following drugs EXCEPT:
A. Paracetamol
B. Acetylsalicylic acid
C. Codiene
D. Ketorolac
E. Dipyrone

11. Which one of the following non-narcotic agents inhibits mainly cyclooxygenase (COX) in CNS?
A. Paracetamol
B. Ketorolac
C. Acetylsalicylic acid
D. Ibuprofen
E. Celecoxib

12. For which of the following conditions could aspirin be used prophylactically?
A. Noncardiogenic pulmonary edema
B. Peptic ulcers
C. Thromboembolism
D. Metabolic acidosis
E. Periodontitis

13. Nefopam:
A. Is associated with gastrointestinal haemorrhage
B. Causes miosis
C. Causes more respiratory depression than morphine
D. Potentiates the dysrhythmogenic effect of halothane anaesthesia
E. Is contraindicated in epilepsy

14. Indicate the benzodiazepine, which has the shortest elimination half-life:
A. Nitrazepam
B. Alprazolam
C. Triazolam
D. Diazepam
E. Clorazepate

15. Which of the following benzodiazepines is preferred for elderly patients?
A. Clorazepate
B. Clonazepam
C. Triazolam
D. Prazepam
E. Diazepam

16. Which of the following benzodiazepines is preferred for patients with liver disease?
A. Clorazepate
B. Nitrazepam
C. Lorazepam
D. Prazepam
E. Diazepam

17. The following drug can be given to reverse benzodiazepine overdose:
A. Cocaine
B. Flumazenil
C. Buspirone
D. Picrotoxin
E. Diazepam

18. Indicate the anxiolitic agent, which relieves anxiety without causing marked sedative effects:
A. Diazepam
B. Buspirone
C. Lorazepam
D. Clorazepate
E. Zolpidem

19. Local anesthetics produce:
A. Analgesia, amnesia, loss of consciousness
B. Blocking pain sensation without loss of consciousness
C. Alleviation of anxiety and pain with an altered level of consciousness
D. A stupor or somnolent state
E. Physical dependence

20. Local anesthetics act by:
A. Blocking voltage-gated sodium channels
B. Blocking voltage-gated calcium channels
C. Blocking voltage-gated potassium channels
D. Blocking chloride conductance
E. Blocking NMDA receptors

21. Which of the following local anesthetics has short duration?
A. Procaine
B. Mepivacaine
C. Prilocaine
D. Lidocaine
E. Tetracaine

22. Which drug does not activate opioid receptors, has been proposed as a maintenance drug in treatment programs for opioid addicts, and with a single oral dose, will block the effects of injected heroin for up to 48 h?
(A) Fentanyl
(B) Nalbuphine
(C) Naloxone

(D) Naltrexone
(E) Propoxyphene

23. Which drug is a full agonist at opioid receptors with analgesic activity equivalent to morphine, a longer duration of action, and fewer withdrawal signs on abrupt discontinuance than morphine?
(A) Fentanyl
(B) Hydromorphone
(C) Methadone
(D) Nalbuphine
(E) Oxycodone

24. Which drug used in the maintenance treatment of patients with tonic-clonic or partial seizure states increases the hepatic metabolism of many drugs including both phenytoin and warfarin?
(A) Buspirone
(B) Clonazepam
(C) Eszopiclone
(D) Phenobarbital
(E) Triazolam

25. A patient with liver dysfunction is scheduled for a surgical procedure. Lorazepam or oxazepam can be used for preanesthetic sedation in this patient without special concern regarding excessive CNS depression because these drugs are
(A) Actively secreted in the renal proximal tubule
(B) Conjugated extrahepatically
(C) Eliminated via the lungs
(D) Reversible by administration of naloxone
(E) Selective anxiolytics like buspirone

26. This drug used in the management of insomnia facilitates the inhibitory actions of GABA. Its actions are antagonized by flumazenil.
(A) Buspirone
(B) Temazepam
(C) Eszopiclone
(D) Ramelteon
(E) Phenobarbital

27. A 9-year-old child is having learning difficulties at school. He has brief lapses of awareness with eyelid fluttering that occur every 5–10 min. Which drug would be effective in this child without the disadvantages of excessive sedation?
(A) Clonazepam
(B) Diazepam
(C) Ethosuximide
(D) Gabapentin
(E) Phenobarbital

28. Which antiepileptic drug is most likely to elevate the plasma concentration of other drugs administered concomitantly?
(A) Carbamazepine
(B) Clonazepam
(C) Phenobarbital
(D) Phenytoin
(E) Valproic acid

29. With chronic use in seizure states, the adverse effects of this drug include coarsening of facial features, hirsutism, and gingival hyperplasia.
(A) Carbamazepine
(B) Ethosuximide
(C) Zonisamide
(D) Tiagabine
(E) Phenytoin

30. The mechanism of antiseizure activity of carbamazepine is
(A) Block of sodium ion channels
(B) Block of calcium ion channels
(C) Facilitation of GABA actions on chloride ion channels
(D) Glutamate receptor antagonism
(E) Inhibition of GABA transaminase

31. Which statement about phenytoin is accurate?
(A) Displaces sulfonamides from plasma proteins
(B) Drug of choice in myoclonic seizures
(C) Half-life is increased if used with phenobarbital
(D) Isoniazid (INH) decreases steady-state blood levels of phenytoin
(E) Toxic effects may occur with only small increments in the dose

32. Which of the following drugs is the most effective in the emergency management of malignant hyperthermia?
(A) Atropine
(B) Dantrolene
(C) Haloperidol
(D) Succinylcholine
(E) Vecuronium

33. Which drug is most likely to cause hyperkalemia leading to cardiac arrest in patients with spinal cord injuries?
(A) Baclofen
(B) Dantrolene
(C) Pancuronium
(D) Succinylcholine
(E) Vecuronium

34. Tolcapone may be of value in patients being treated with levodopa-carbidopa because it:
(A) Activates COMT
(B) Decreases the formation of 3-*O*-methyldopa
(C) Inhibits monoamine oxidase type A
(D) Inhibits neuronal reuptake of dopamine
(E) Releases dopamine from nerve endings

35. Concerning the drugs used in parkinsonism, which statement is accurate?
(A) Dopamine receptor agonists should never be used in Parkinson's disease before a trial of levodopa
(B) Levodopa causes mydriasis and may precipitate an acute attack of glaucoma
(C) Selegiline is a selective inhibitor of COMT
(D) The primary benefit of antimuscarinic drugs in parkinsonism is their ability to relieve bradykinesia
(E) Therapeutic effects of amantadine continue for several years

36. Which drug is an antagonist at 5-HT2 receptors and can be used for the management of insomnia?
(A) Estazolam
(B) Flurazepam
(C) Trazodone
(D) Triazolam
(E) Zolpidem

37. Which of the following drugs is most likely to be of value in obsessive-compulsive disorders?
(A) Amitriptyline
(B) Bupropion
(C) Sertraline
(D) Trazodone
(E) Venlafaxine

38. A patient under treatment for a major depression is brought to the emergency department after ingesting 30 tablets of imipramine. Which of the following would be LEAST useful?
(A) Administer bicarbonate to correct acidosis.
(B) Administer lidocaine to control cardiac arrhythmias.
(C) Initiate hemodialysis to hasten drug elimination.
(D) Maintain heart rhythm by electrical pacing
(E) Use intravenous diazepam to control seizures

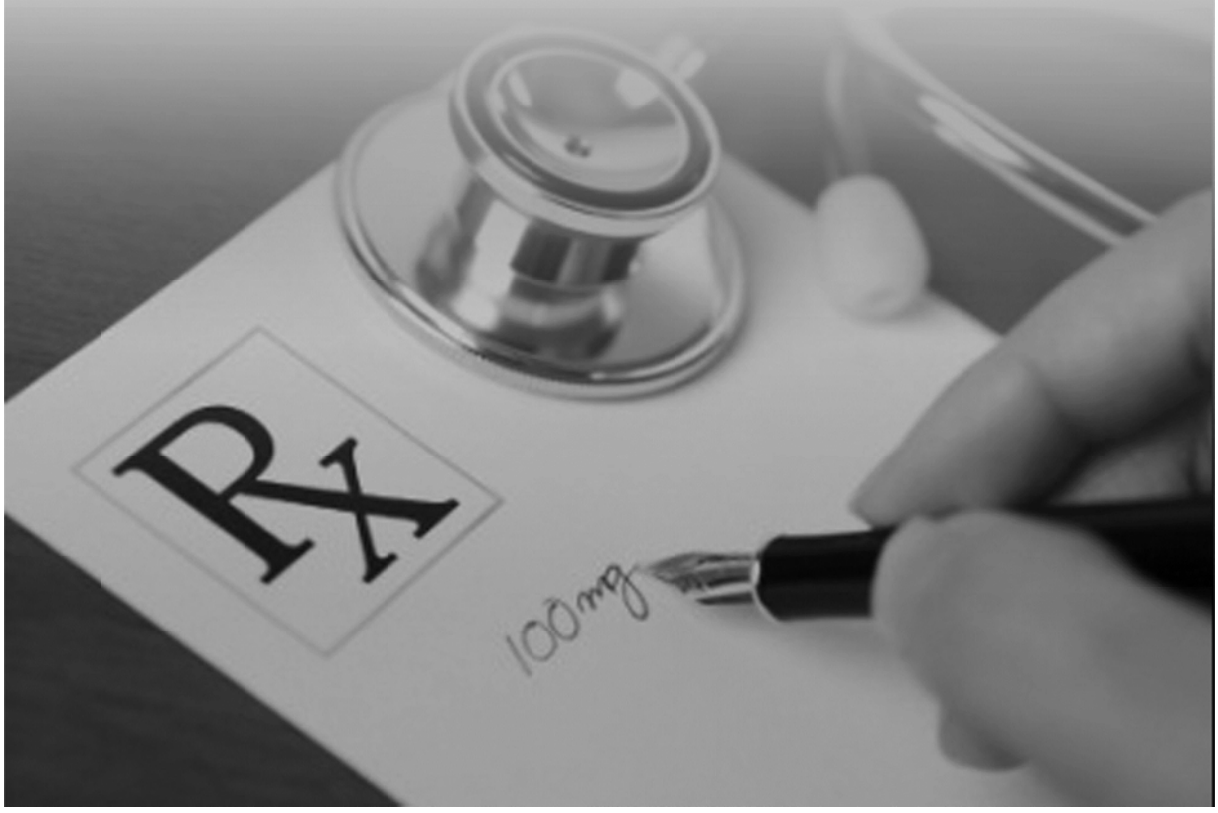
39. A 36-year-old woman presents with symptoms of major depression. Drug treatment is to be initiated with sertraline. In your information to the patient, you would tell her that
(A) Sertraline may take 2 wk or more to become effective
(B) It is preferable that she take the drug in the morning
(C) Muscle cramps and twitches can occur
(D) She should notify you if she anticipates using other prescription drugs
(E) All of the above

Answers

1 C	10 C	19 B	28 E	37 C
2 E	11 A	20 A	29 E	38 C
3 A	12 C	21 A	30 A	39 E
4 E	13 E	22 D	31 E	
5 A	14 C	23 C	32 B	
6 D	15 C	24 D	33 D	
7 A	16 C	25 B	34 B	
8 C	17 B	26 B	35 B	
9 D	18 B	27 C	36 C	

Chapter 11

Antimicrobial Drugs



Chapter 11

Antimicrobial Drugs

Part 1: Basic Principles of Antimicrobial Drugs

Chemotherapy is the killing of a living organism whether being bacteria, fungi, protozoa, or virus.

Bacteria are prokaryotic cells. Some bacteria are pathogenic to humans and can cause serious infections; the principal treatment of infections is with **antibiotics**.

CLASSIFICATION OF ANTIMICROBIAL DRUGS

A. According to source:

- **Natural compounds**: e.g. *penicillin, chloramphenicol.*
- **Synthetic compounds**: e.g. *sulfonamides, quinolones.*
- **Semisynthetic compounds:** e.g. *ampicillin.*

B. According to the effect on microorganisms:

- **Bactericidal agents:** that kills the microorganism e.g. *penicillin.*
- **Bacteriostatic agents:** arrest growth of the microorganism e.g. *sulfonamides.*

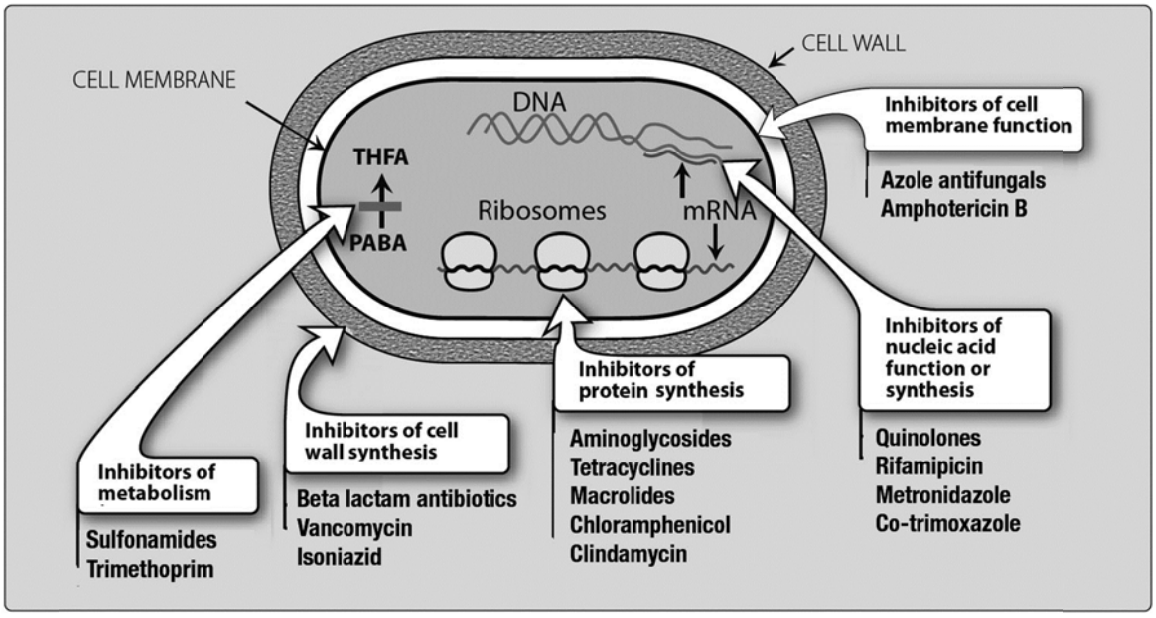
C. According to mechanism of action:

- Agents act by inhibition of **cell wall** synthesis: e.g. *penicillin.*
- Inhibition of **cell membrane** function e.g. *amphotericin B and azoles.*
- Agents act by inhibition of **nucleic acid** synthesis: e.g. *quinolones.*
- Agents act by inhibition of **protein** synthesis:
  - *By acting on ribosomal **30 S** subunit e.g. aminoglycosides.*
  - *By acting on ribosomal **50 S** subunit e.g. macrolides.*
- Agents act by inhibition of bacterial **metabolism**: e.g. *sulfonamides.*

D. According to antimicrobial spectrum:

Species pluralis (spp.), Latin abbreviation for multiple species.

- **Narrow spectrum drugs:**
  - Drugs affect mainly Gram +ve spp. e.g. *benzyl penicillin*.
  - Drugs affect mainly Gram –ve spp. e.g. *aminoglycosides.*
- **Extended spectrum drugs:** agents that affect Gram +ve & Gram –ve spp..
- **Broad spectrum drugs:** agents act on wide range of Gram +ve & Gram –ve spp. and others (protozoa) e.g. *tetracyclines.*



COMBINATION OF ANTIBIOTICS

Indications:

- To obtain broader **spectrum** e.g. *amoxicillin + clavulanic acid → co-amoxiclav.*
- To obtain **synergism** e.g. sulfonamides + trimethoprim → *co-trimoxazole.*
- In **mixed** bacterial infections e.g. diabetic foot or peritonitis.
- In **serious** bacterial infections e.g. bacterial meningitis or septicemia.
- To overcome **bacterial resistance** e.g. TB and pseudomonas infection.
- To **reduce toxicity** of one drug by using smaller doses of two drugs.

Results:

- Bactericidal + bactericidal → **synergism:** e.g. penicillin with aminoglycosides.
- Bacteriostatic + bacteriostatic → **addition:** e.g. tetracyclines with sulfonamides.
- Bactericidal + bacteriostatic → **antagonism or synergism:**
  - **Antagonism:** when bacteri**cidal** drug acts by inhibiting cell wall synthesis (i.e. kills rapidly multiplying bacteria e.g. penicillin) is combined with

bacterio**static** drug (e.g. erythromycin) which arrests the organism and prevents its multiplication.

- **Synergism:** in special cases e.g. combination between **sulfadiazine** + **penicillin** in meningococcal meningitis (both drugs attain high concentrations in CSF when meninges are inflamed).

CLINICAL APPROACHES FOR RATIONAL PRESCRIBING OF ANTIBIOTICS

A. Confirm the presence of an infection

Fever:

- Fever is considered a hallmark of most infectious diseases.
- Fever is defined as repeated oral temperatures > 37.2 ◦C.
- Fever may be **present in absence of infection** e.g. in autoimmune disorders and several malignancies.
- Fever may be **absent in presence of infection** if the immune system is depressed.

White blood cell count:

- Normal WBC is 4000-10,000 cells/mm3.
- **Bacterial** infections are associated with elevated **granulocyte** counts (neutrophils, basophils, and eosinophils).
- **Viral, TB** and **fungal** infections are associated with elevated **lymphocytic** count.
- **Parasitic** infections and **allergic** reactions are associated with increased **eosinophilic** count.

B. Selection of antimicrobial agents

Identification of the infecting organism:

- Infected body materials (e.g., blood, sputum, urine, wound drainage, etc.) must be sampled and cultured **before** initiating treatment.
- **Empirical therapy** before identification of the organism is necessary in the following conditions:
  - In all **acutely ill patients** with infections of unknown origin.
  - Infection in a **neutropenic** patient, or a patient with **meningitis** *(characteristically described by severe headache, neck rigidity, and sensitivity to bright lights)*. In such conditions any delay in the treatment could be fatal.

- **Patient factors:**

- **In neonates**, the use of *chloramphenicol* can lead to shock and cardiovascular collapse (gray baby syndrome) because liver functions are not well developed. Also, the use of *sulfonamides* may lead to kernicterus (brain damage) due to displacement of bilirubin from serum albumin.
- **In growing children**, the use of *fluoiroquinolones* can lead to arthropathy (joint swelling, stiffness and cartilage damage). Also, the use of *tetracyclines* can bind to growing bones and teeth resulting in abnormal teeth and bone formation.
- **In old age** (> 65 years) the incidence of renal toxicity with *aminoglycosides* is greater than in younger patients.
- **In immunocompromised patients**, the use of **bactericidal** agents is necessary, as the host's immune system is not capable of final elimination of the bacteria.
- **Pregnancy:** many antibiotics cross the placenta and cause adverse effects to the fetus e.g. *aminoglycosides* and *tetracyclines*.

- **Tissue penetration:**

- The capillary lining in some tissues, e.g. prostate, the vitreous body of the eye, and brain form **natural barriers** to drug delivery due to presence of tight junctions of the capillary wall.
- Lipid soluble antibiotics e.g. *chloramphenicol* and *metronidazole* can cross these barriers in normal conditions. *Penicillin* is ionized at physiologic pH and cannot cross these barriers unless **inflammation** is present.
- **Poor perfusion** of some area, e.g. diabetic foot, reduces the amount of antibiotic reaching this area, making treatment is difficult.

C. Determinants of the rational dosing

The dose and frequency of an antibiotic is based on three important properties. Understanding of these concepts can improve clinical outcomes and decrease the development of resistance.

- **Concentration-dependent killing:**

Certain antibiotics *(e.g. aminoglycosides)* show enhanced bacterial killing in concentration above the MIC. Giving these antibiotics by a **single large dose** per day achieves high peak levels and cause rapid killing of bacteria.

Minimum inhibitory concentration (MIC):

The MIC is the lowest concentration of antibiotic in body tissues and fluids that inhibits bacterial growth.

- **Time-dependent killing:**

By contrast, *β-lactam antibiotics, macrolides, clindamycin,* and *linezolid* do not exhibit this concentration-dependent property; instead, the clinical efficacy depends on the **time** of the drug concentration remains above the MIC. So, preparations with long duration kill more bacteria.

- **Post-antibiotic effect (PAE):**

The PAE is a persistent bacterial suppression after levels of antibiotic fall below the MIC. Antimicrobials with long PAE (e.g. *aminoglycosides* and *fluoroquinolones*) usually require one dose per day.

ANTIBIOTIC RESISTANCE

The development of antibiotic resistance is a major problem in clinical practice. Methicillin-resistant *Staph aureus* (MRSA) and some strains of *Mycobacteria tuberculosis* are examples of multidrug-resistant bacteria.

- **Innate resistance:**

Innate resistance is a feature of a particular species of bacteria e.g *Pseudomonas*. The gene(s) of resistance can be transferred between bacteria by transfer of naked DNA (transformation), by conjugation with direct cell-to-cell transfer of extrachromosomal DNA (plasmids), or through bacteriophage (transduction).

- **Acquired resistance:**

Acquired resistance is when bacteria that were sensitive to certain antibiotic become resistant with time. Mechanisms responsible for this resistance include:

- Production of enzymes that inactivate the drug.
- Alteration of drug binding site.
- Reduction in drug uptake by the organism.
- Development of altered metabolic pathways.

ADVERSE EFFECTS OF ANTIMICROBIAL AGENTS

The adverse effects associated with the use of antimicrobial agents include:

- <u>General adverse effects</u>

- **Hypersensitivity** or allergic reactions: In form of fever, skin rash, arthralgia, cholestatic jaundice or hemolysis. More serious reactions are agranulocytosis, bone marrow aplasia or anaphylactic reaction.

- Reactions related to alterations in normal body flora, **superinfection or vitamin B deficiency** may follow the use of broad-spectrum antimicrobials. It is due to inhibition of bacterial flora that suppresses commensal micro-organisms which present in gut or that forms these vitamins, respectively.
- **Resistance**

- **Direct toxic reactions,** resulting from high doses or drug interactions, on hemopoietic system, liver, kidney, GIT, nervous system or CVS.

SUPERINFECTION (Opportunistic infection):

Administration of antimicrobials usually alter bacterial flora but with no ill effect in most cases however, broad-spectrum antibiotics if used for long time may alter or kill bacterial flora. So, the bacteria and fungi that are normally inhibited by bacterial flora will multiply leading to superinfection (its early manifestation may by diarrhea). It is caused by staphylococci, Pseudomonas, proteus, Candida albicans or *Clostridia difficile...* etc. Superinfection may be vaginal, oral, pharyngeal or even systemic infection e.g. staphylococcal enterocolitis, candidiasis or Pseudomembranous colitis (= antibiotic-associated diarrhea).

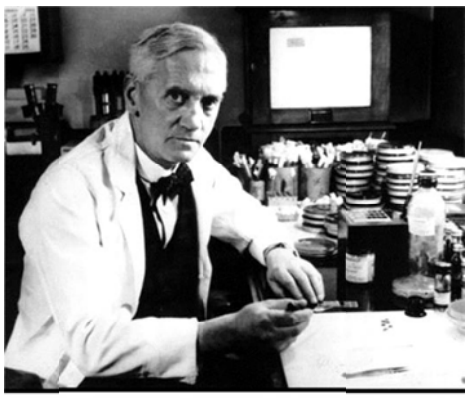
Treatment:
Stop the causative agent and give drug, which kill the organisms responsible for superinfection e.g. staphylococcal enterocolitis, which is treated by **metronidazole or vancomycin** orally, antifungal nystatin for candidiasis.

GENERAL PRINCIPLES OF THERAPY WITH ANTIMICROBIALS

- Antimicrobials should only be given when necessary and after antimicrobials susceptibility test whenever possible.
- The pharmacokinetics of the drug should be taken into consideration e.g. the state of hepatic and renal functions of the patient.
- In serious infection it is better to start with a parentral loading of a bactericidal agent to avoid emergence of resistant strains by giving adequate dosage for sufficient duration and adapting proper combination regimens.
- Antimicrobials should be continued for 3 days after apparent cure is achieved to avoid relapse.

Part 2: Individual Classes of Antibiotics

A. CELL WALL INHIBITORS

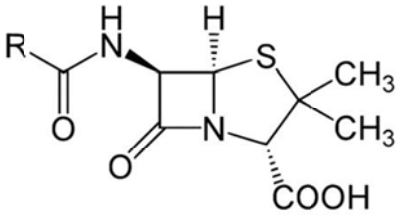


Alexander Fleming, who is credited with discovering penicillin in 1928

β-LACTAM ANTIBIOTICS

They share a β-lactam ring in their molecular structure which is required for antibacterial activity.

- **Penicillin**
- **Cephalosporins**
- **Monobactams**
- **Carbapenem**



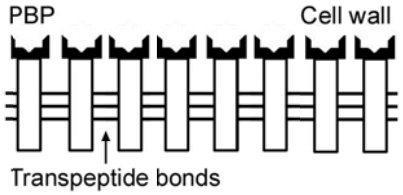
Penicillin core structure, where "R" is the variable group

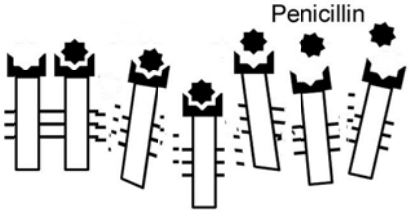
Penicillins

Antibacterial spectrum:

- *Gram-positive cocci,* e.g. streptococci, pneumococci and staphylococci.
- *Gram-negative cocci:* gonococci and meningococci.
- *Gram-positive bacilli:* anthrax bacillus, C. diphtheria and clostridia.
- *Gram-negative bacilli:* shigella, salmonella, pseudomonas…etc.
- *Spirochetes:* Treponema pallidum.
- *Actinomyces.*

Mechanism of action:





- Penicillins bind to **penicillin binding proteins** (PBPs) on the bacterial cell wall and inhibit transpeptidation reaction essential for **bacterial cell wall synthesis.**
- The next step is activation of intracellular autolytic enzymes (**autolysins**) leading to cell rupture. *Thus, the antibacterial effect of penicillin is the result of both inhibition of cell wall synthesis and destruction of existing cell wall by autolysins.*
- Penicillins are **bactericidal** especially for **Gram-positive** bacteria which have thick cell walls.
- The major cause of resistance is the production of **β-lactamase** *(penicillinase)*.

Pharmacokinetics:

- Absorption of oral penicillins is decreased by food. They must be administered **1**hr before or 2 hr after meals.
- Route of administration of a B-lactam antibiotic is determined by the stability of the drug to gastric acid and by the severity of the infection.
  - Oral in moderate infection and acid stable preparations e.g. penicillin V.
  - Paraentral in severe infection and acid sensitive preparations e.g. penicillin G
- Penicillins can penetrate to CSF and ocular fluid only during meningitis. They cross placental barrier but they are not teratogenic.
- Most penicillins are excreted through organic acid secretory system via the kidney. The renal excretion in proximal tubules could be decreased by co-administration of probenecid which prolongs its duration of action.

PREPARATIONS OF PENICILLINS:

1.BENZYL PENICILLIN (PENICILLIN G) and RELATED DRUG:

Effectiveness: active against gram-negative and positive cocci, gram-positive bacilli and spirochetes. It is sensitive to penicillinase enzyme.

Classification:

A. Injectable Short-acting preparation e.g. benzyl penicillin (penicillin-G):

- It is the prototype of all penicillin family.
- Primarily covers **gram-positive organisms** (*Pneumococci, streptococci, staphylococci (*non-penicillinase-producing)*, Cl. perfringens,C. diphtheria*) with **little gram-negative** coverage (*Gonococci* and *meningococci[but not bacilli]*), making it **ineffective** in urinary tract infection.
- ***Others:*** *Treponema pallidum* (syphilis).
- It has some limitations:
  - It is acid labile and must be given parentrally.
  - It has a short half-life, so frequent injections are required.
  - It is easily inactivated by β-lactamase enzyme.
  - It has narrow spectrum.

B. Injectable Long-acting preparation

i. Penicillin G Procaine:

It is a suspensions of combination of penicillin G with procaine that have longer duration (12-24 hrs) allowing reduced frequency of injections. So it is injected just once every day, intramuscularly.

ii. Benzathine Penicillin: This preparation produces low blood levels lasting from few days to 4 weeks depending on the dose. So it is used in chemoprophylaxis and in the treatment of syphilis.

C. Oral Penicillin V: it is an acid stable form of penicillin G (given orally).

2. PENICILLINASE OR β-LACTAMASE RESISTANT PENICILLINS (ANTI-STAPH PENICILLINS)

[Methicillin, cloxacillin, dicloxacillin, flucloxacillin, and **nafcillin]**

- They are effective against β-lactamase producing *Staphylococci*.
- They have low or **no activity** against **other gram-positive and gram-negative organisms**.
- The use of these agents is now declining due to increased incidence of methicillin-resistant *S. aureus* (MRSA).

3. EXTENDED SPECTRUM PENICILLINS

[Ampicillin and **amoxicillin]**

- They maintain gram-positive coverage with extended coverage of more **gram-negative bacteria** e.g. *Salmonella*, H. influenza, Proteus, and Shigella (but not *Pseudomonas*).
- They can be given orally (acid resistant) and by injection (IM and IV).
- They are inactivated by β-lactamase, so they are usually combined with **clavulanic acid** or **sulbactam** (β-lactamase inhibitors) to cover β-lactamase producing bacteria. **[Amoxicillin/clavulanic acid** (co-amoxiclav) - **Ampicillin/sulbactam** (Unasyn)].
- **Ampicillin** is concentrated in bile so it is effective in gall bladder disease and typhoid carrier.
- **Ampicillin**is more active on shigella and H. influenza.
- **Pro-drugs of ampicillin** e.g. pivampicillin and talampicillin are esters of ampicillin which themselves are microbiologically inactive but after oral administration they are de-esterified in the gut mucosa or liver to release ampicillin to the systemic circulation. They are better absorbed from the gut than ampicillin itself, so gives higher levels in blood and tissues and they have no effect on the gut flora and less G.I. upset.
- **Amoxicillin** has better absorption and tissue penetration than ampicillin. So, it has no effect on the gut flora and less G.I. upset.

Common organisms capable of producing penicillinase:

Staphylococcus aureus,
Escherichia coli,
H. influenzae
Pseudomonas aeruginosa
Neisseria gonorrhoeae
Proteus
*Bacteroides*species.

- **Amoxicillin** is more active against Salmonella and Streptococcal fecalis.
- **Amoxicillin** can penetrate mucoid and purulant sputum, so it is useful in chronic bronchitis.

4. ANTIPSEUDOMONAL PENICILLINS

[Ticarcillin, Azlocillin, and **Piperacillin]**

- They are broad-spectrum, but should only be used for pseudomonas infection and ampicillin resistant proteus. Also they have activity against anaerobic gram negative bacteria e.g. Bacteroids fragilis (a common pathogen in intra-abdominal sepsis)
- They have synergistic effect when they are used with aminoglycosides.
- They are inactivated by β-lactamase so they are combined with **clavulanic acid forming Timentin** to cover β-lactamase producing bacteria.

	PENICILLIN G	ANTI-STAPH PENICILLINS	EXTENDED SPECTRUM PENICILLINS	ANTI-PSEUDOMONAL PENICILLINS
		Cloxacillin Flucloxacillin Nafcillin	**Ampicillin Amoxicillin**	**Ticarcillin Azlocillin Pipracillin**
Spectrum	Gram +ve spp. and few Gram –ve *cocci* *T. pallidum*	*Staphylococci*	Gram +ve and Gram –ve spp. (except *Pseudomonas*)	*Pseudomonas* and Gram –ve spp.
β-lactamase susceptibility	Yes	No	Yes	Yes
			They are combined with **clavulanic acid or sulbactam** to cover β-lactamase producing bacteria.	

Therapeutic uses of penicillins:

A. Treatment: Penicillins may be used in the treatment of:

- Streptococcal infections, e.g. wound sepsis, acute throat infections, subacute bacterial endocarditis,.. etc.
- Staphylococcal infections of skin, mucous membrane and bone.
- Pneumococcal infections e.g. pneumonia.
- Syphilis (5 million units single dose) and gonorrhoea.
- Meningococcal infections: Penicillin diffuses into the CSF only when the meninges are acutely inflamed.
- Typhoid and paratyphoid fevers: ampicillin and amoxycillin.

- Pseudomonas infection: (ticarcillin or piperacillin)
- Actinomycosis, Anthrax and H. influenza infections.
- Diphtheria, tetanus and gas gangrene. (Penicillin may be used together with the specific antitoxins).

B. Prophylaxis: Penicillins may be used prophylactically in the following conditions:

- To prevent recurrence of rheumatic fever: Benzathine penicillin, 1.2 million units IM once a month.
- To prevent subacute bacterial endocarditis due to bacteraemia resulting from operative procedures such as dental extraction, tonsillectomy…etc. in patients with congenital or acquired valvular disease or immunocompromised patient.

Adverse effects:

- **Hypersensitivity reactions:**
  - It occurs in ~10% of patients receiving penicillin.
  - It occurs with all types of penicillin. Allergy is not due to penicillin itself but to degradation product common to all penicillin
  - It is more common after parenteral than oral administration.
  - All types of reactions, from simple rash to **acute anaphylaxis and angioedema**, can occur within 2 minutes (**early or type I** hypersensitivity) or up to 12 days (**delayed or type II**) after administration.

  - True anaphylaxis is rare (1:10'000 of cases).
  - Penicillin allergy is unpredictable i.e. an individual who tolerated penicillin in the past may develop allergy later on and *vice versa.*

  Prevention:
  - Never give penicillin if there is history of penicillin allergy.
  - Test for hypersensitivity

  Management of anaphylactic shock: see CVS.

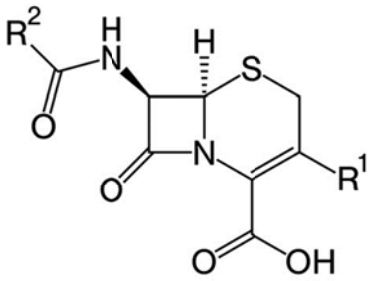
- **Other adverse effects:**
  - Penicillin in high doses can cause neurotoxicity and seizures in patients with renal failure.
  - Nafcillin is associated with neutropenia and thrombocytopenia.
  - Methicillin causes interstitial nephritis (and is no longer used for this reason).
  - Co-amoxiclav and flucloxacillin cause hepatotoxicity (cholestatic jaundice).

Drug interactions:

- **Bacteriostatic drugs** (e.g. tetracycline, chloroamphenicol, erythromycin) interfere with the action of penicillin because penicillin acts by inhibiting cell wall synthesis (i.e. kills rapidly multiplying bacteria) while bacterio**static** drugs arrest the organism and prevents its multiplication.
- **Antipseudomonal penicillins** (acidic drugs, —ve charged) form complex with **aminoglycosides** (basic drugs, +ve charged) if they are mixed in the same infusion fluid.

Cephalosporins

- Cephalosporins also have a **β-lactam** ring and have the **same mechanisms** of action like penicillins.
- Each newer generation of cephalosporins is increasingly **resistant to β-lactamase.**



Core structure of the cephalosporin antibiotics

Pharmacokinetics:

- Cephalosporins are widely distributed in body fluids; members of the third and fourth generations can penetrate to CSF *(except cefoperazone)*.
- Like penicillins, most cephalosporins are excreted via the kidneyand hence the dose must be adjusted in patient with renal insufficiency. The renal excretion is also decreased by probenecid.
- Cefoperazone and ceftriaxone (third generation) are primarily excreted in bile and its serum level is not greatly influenced by renal failure.

Antibacterial spectrum And Classification:

They are divided into 1st, 2nd, 3rd, and 4th generations. The difference among the groups is marked by changes in antibacterial spectrum. In general, the activity against gram-positive bacteria decreases from first to third generation while activity against gram-negative organisms increases.

1. First-generation cephalosporins:

[Cephalexin (Keflex), **cephradine** (Velosef), **cefadroxil** (Duricef)].

- Primarily cover **gram-positive organisms** (similar to penicillin G) with **some gram-negative coverage** (*E. coil, Klebsiella*), making them **effective** in urinary tract infection.
- They are **sensitive to β-lactamase.**
- They **do not penetrate to CSF** (even in presence of meningitis).
- There is partial cross allergenicity between them and penicillins.

2. SECOND-GENERATION CEPHALOSPORINS

[Cefoxitin, **cefuroxime** (Zinnat), **cefaclor**].

- They maintain gram-positive coverage with enhanced coverage of gram**-negative bacteria** e.g. *H. influenza, Neisseria, Proteus,* (but not *Pseudomonas*).
- They are used primarily in the management of **urinary and respiratory tract, bone, and soft-tissue infections** and **prophylactically** in various surgical procedures.
- They are relatively resistant to β-lactamases.
- They **do not penetrate to CSF** (even in presence of meningitis, *except cefuroxime*).

3. THIRD-GENERATION CEPHALOSPORINS

[Cefotaxime (Clarofan), **Ceftazidine**, **Cefoperazone** (Cefobid), **Ceftriaxone** (Rocephin)

- They maintain gram-positive coverage with excellent coverage of **gram-negative bacteria**(including *Pseudomonas*)and active against **anaerobes.**
- They can **penetrate to CSF** in presence of meningitis *(except cefoperazone).*
- They are excreted by the kidney, except *cefoperazone*and *ceftriaxone* which are excreted **biliary** allowing their use in **renal failure**.
- They are highly resistant to β-lactamase.
- They have long duration (12 hrs) and ceftriaxone has longer duration (24 hrs)

4. FOURTH-GENERATION CEPHALOSPORINS

- **Cefepime** has a powerful coverage against most **Gram-positive** and **Gram-negative bacteria** (including *Pseudomonas*) and **anaerobes.**
- **Ceftaroline** is sometimes described as **"FIFTH GENERATION"** drug. **.**

Therapeutic uses:

- Severe undiagnosed sepsis especially in immunosuppressed patient.
- Treatment of infection of respiratory tract, urinary tract, skin, soft tissue, bones and joints due to susceptible organisms.
- Gram-negative bacterial meningitis may be treated by cefotaxime (third generation) and ceftriaxone that reach the C.N.S.
- Biliary infection: 3rd generation (cefoperazone or ceftriaxone).
- Gonorrhoea due to penicillin-resistant Gonococci. It is treated by single IM injection of ceftriaxone.
- Pseudomonal infection when aminoglycosides are not desirable.

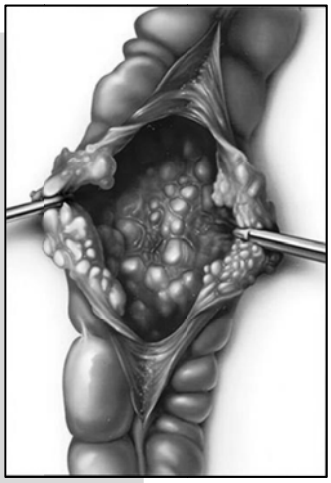
	1ST GENERATION	2ND GENERATION	3RD GENERATION	4TH GENERATION
	Cephalexin Cephradine Cefadroxil	**Cefoxitin Cefuroxime Cefaclor**	**Cefotaxime Cefoperazone Ceftriaxone**	**Cefipime**
Spectrum	Mainly Gram +ve spp. and few Gram –ve bacilli	Maintain Gram +ve coverage and enhanced Gram –ve coverage	Excellent Gram –ve coverage (including *Pseudomonas*)	Wide Gram +ve and Gram –ve coverage including *Pseudomonas*
β-lactamase susceptibility	Yes	Yes	No	No
Penetration to CSF	No even in meningitis	No *(except cefuroxime)*	Yes *(except cefoperazone)*	Yes
Cross allergy with penicillin	High	Moderate	Low	Low
Elimination	Renal	Renal	Renal & biliary	Renal & biliary

Adverse effects:

- **Hypersensitivity reactions**: 10% of penicillin-sensitive persons share hypersensitivity to cephalosporins. The cross hypersensitivity with penicillin is much lower with the 3rd and 4th generation drugs.
- Some **first generation** cephalosporins are **nephrotoxic** especially when administered with loop diuretics or aminoglycosides.
- Some **third generation** cephalosporins (e.g. cephoperazone) inhibit the enzyme *vitamin K epoxide reductase* leading to **hypoprothrombinemia** (could be prevented by vitamin K).
- **Superinfection with *C. difficile* (pseudomembranous colitis):** Cephalosporins are the main cause of hospital-acquired *C. difficile* colitis, a potentially life-threatening infection.

Pseudomembranous colitis

Pseudomembranous colitis (= antibiotic-associated diarrhea or *C. difficile* colitis), can occur following antibiotic treatment. When antibiotics are given, most of the resident intestinal bacteria are killed with sparing of some types like *Clostridia difficile*. The normally harmless *C. difficile* grow rapidly because of lack of competition with other flora, and produce toxins. These toxins damage the inner wall of the intestines and cause abdominal pain, fever and diarrhea. Severe cases can be life-threatening.



Treatment:
- Stop all antibiotics whenever possible.
- Oral **metronidazole** 250 mg /6 hr (1st choice).
- If metronidazole failed, give oral **vancomycin** solution 125 mg/6 hr

Drug interactions:

- If IV **ceftriaxone** is added to any IV **calcium-containing solution** (e.g. Ringer's or parenteral nutrition) dangerous particulates of **ceftriaxone-calcium** can result and precipitate in the lungs and kidney. Separate between IV ceftriaxone and any IV calcium-containing solution by at least 48 hours.
- Some **third generation** cephalosporins inhibit the enzyme *aldehyde dehydrogenase*. If they are co-administered **with alcohol**, acetaldehyde accumulates in blood leading to nausea and vomiting (**disulfiram-like reaction**).

OTHER beta-LACTAM DRUGS

Aztreonam (Azactam)

- Aztreonam is a monobactam that share similarity in structure and mechanism with penicillin but is highly **resistant to β-lactamase.**
- Aztreonam is especially effective against β-lactamase producing **gram-negative bacteria**. It could be used as alternative to aminoglycosides in **severe** respiratory, urinary, biliary, GIT and female genital tracts infections.
- It has **no cross-hypersensitivity** with penicillins or cephalosporins.
- Most of the Adverse effects reported have been, for example, hematological effects, nephrotoxicity and pseudomembranous colitis,.

Carbapenems [Imipenem-cilastatin, meropenem]

- They are **broad spectrum** antibiotics that share similarity in structure and mechanism with penicillin but they are highly **resistant to β-lactamase.**
- They are one of the **antibiotics of last resort** for many bacterial infections.
- The ease of penetration (due to its low molecular weight) and resistance to β-lactamase imparts a broad-spectrum of antimicrobial activity against most aerobic and anaerobic bacteria (Gram-positive and gram-negative) with the exception of occasional Pseudomonas strains.
- If imipenem is given alone it is inactivated by dihydropeptidase enzyme in kidney leading to low urinary excretion and significant renal toxicity in animals, therefore it is combined with **cilastatin** (Tienam) to inhibit renal dihydropeptidase enzyme.
- **Meropenem** does not undergo metabolism by renal dihydropeptidase enzyme.

Adverse effects:

- Blood disorders.
- Seizures in high doses. Meropenem is less likely to provoke seizures.
- G.I.T: nausea, vomiting, etc.

OTHER CELL WALL INHIBITORS

Vancomycin

- Vancomycin **inhibits cell wall synthesis** and enhances cell lysis.
- It is active against **gram-positive organisms.**
- It is given by slow i.v. infusion to treat **serious MRSA infections** in patients allergic to penicillins or cephalosporins.
- Because it is not absorbed orally, it is used by this route to treat **antibiotic-associated enterocolitis** (*C. difficile* colitis) and other infection by susceptible organisms.
- Rapid infusion of vancomycin may cause anaphylactoid reactions and **"red man" syndrome** (skin rash and flushing due to histamine release).
- Rarely, high levels of vancomycin may cause permanent auditory impairment (**ototoxicity)** and **nephrotoxicity**.

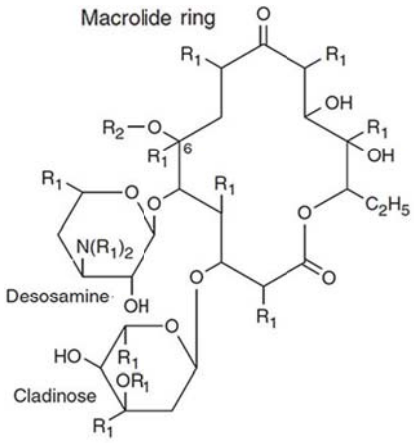
Bacitracin

- Bacitracin inhibits the building of peptidoglycan blocks (cell wall units).
- It is most active against **gram-positive bacteria**.
- It is used **only topically** in combination with **neomycin or polymyxin** for minor skin infections due to serious nephrotoxicity.

B. INHIBITORS OF BACTERIAL PROTEIN SYNTHESIS

Macrolides

[Erythromycin (prototype), azithromycin, clarithromycin, roxithromycin]



Mechanism of action:

- They bind reversibly to the **50S ribosomal subunit** and **inhibit bacterial protein synthesis.**
- They are **bacteriostatic** in low concentrations and bacteri**cidal** in high concentrations.

Antibacterial spectrum:

Macrolids are effective against a number of organisms, including **gram-positive bacteria,** e.g. pneumoncocci, staphylococci, streptococcus species, C. diphtheria, **some gram-negative** bacteria, e.g. Neisseria, H. influenza, and intracellular microorganisms (Mycoplasma species, legionella and Chlamydia).

Pharmacokinetics:

- Absorption of erythromycin is affected by food and HCl. To minimize destruction and enhance absorption, erythromycin is administered as esters salts.
- Newer macrolides are acid stable and can be given orally.
- They reach all body fluids including prostate, placenta and milk but only **small amounts** can penetrate to CSF.
- Azithromycin and roxithromycin are **concentrated** in neutrophils, macrophages and lung tissue, so they have long $t_{1/2}$ (given once daily) and they are useful against **intracellular organisms.**
- Macrolides are concentrated in liver and excreted **primarily in active form via bile** with only low levels found in urine.
- Azithromycin and clarithromycin are converted into **active** metabolites.

Therapeutic uses:

- Treatment and prevention of infections caused by staphylococci, streptococci and pneumococci (**gram-positive**) in penicillin-hypersensitive individuals.
- Eradication of C. diphtheriae from pharyngeal carriers (1st choice).
- Azithromycin and roxithromycin are especially effective against **intracellular** and **atypical bacteria** *(chlamedia, mycoplasma, legionella)*
- **Clarithromycin** has activity against *Toxoplasma*. It is also effective against *Helicobacter pylori* in peptic ulcer**.**
- It is a second line drug for the treatment of gonorrhea and syphilis.
- Treatment of middle ear and sinus infections, since the causative agents, *H. influenza* and *Strep pneumonia* are usually sensitive.

Adverse effects:

- **Epigastric distress** especially with erythromycin.
- Erythromycin may cause **cholestatic hepatitis** probably due to hypersensitivity reaction to the oral estolate form or hepatoxic effect when drug therapy lasts longer than 10 days or repeated courses are prescribed.
- Erythromycin and clarithromycin **inhibit hepatic CYP450**– metabolism of some drugs e.g. warfarin and phenytoin *(Azithromycin is devoid of this side effect)*.
- **Bacterial resistance** if it is used more than one week.
- **Hypersensitivity reactions**: fever, rashes and cholestatic hepatitis.

Interactions:

- Combination of the therapeutic dose of erythromycin with penicillin antagonizes the bactericidal effect of penicillin.
- Erythromycin decreases CYP450 enzymes, thus increase serum concentration of theophylline, oral anticoagulants, cyclosporins, and digoxin.

Lincosamides: Clindamycin

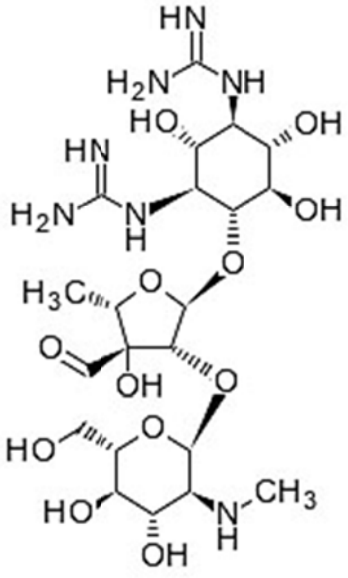
- The lincosamide family of antibiotics includes lincomycin and clindamycin. Clindamycin is semisynthetic derivative of lincomycin and is more potent than lincomycin.
- Clindamycin is similar, in the mechanism and kinetics, to **erythromycin** but has activity against **anaerobic bacteria**.
- It is used as an alternative drug for treatment of **anaerobic infections**. Topical preparations are used for treatment of **acne.**
- Food in the stomach does not interfere with the absorption of clindamycin. So it is completely absorbed after oral administration.
- Approximately 90 % are plasma protein bound. Clindamycin penetrate most tissues well, including bone. Therefore, **bone and joint** infections caused by susceptible organisms respond well to treatment with clindamycin.
- It is associated with high incidence of diarrhea and **pseudomembranous colitis** as side effect due to superinfection by resistant clostridia in addition to side effects of erythromycin.

Aminoglycosides

[streptomycin (prototype), Gentamicin, tobramycin, amikacin, kanamycin, neomycin]

Mechanism of action

- Aminoglycosides are transported across the inner cell membrane by active transport system present **only in Gram-negative aerobic spp**.
- Inside the cell, they bind to **30S ribosomal subunit** and **inhibit bacterial protein synthesis**.
- They are bacteri**cidal.** Bacterial killing is **concentration-dependent** i.e., the higher the concentration, the more bacteria are killed, so they are better given as a single large dose daily.
- A **post-antibiotic effect** is also present *i.e.,* residual bactericidal activity is present after the serum concentration falls below the MIC.



Structure of streptomycin

Antimicrobial spectrum:

They have **narrow spectrum** against mainly **Gram negative bacilli**, very few Gram positive cocci, and Mycobacteria TB.

Pharmacokinetics:

- All aminoglycosides are **not absorbed orally** (must be given parentrally) and **cannot penetrate to CSF** because they are highly **polar** compounds.
- They can cross the **placental barrier** and may cause **congenital deafness**.
- They are excreted **unchanged** in urine by glomerular filtration *(dose adjustment is necessary in renal dysfunction)*. They become more active in **alkaline urine**.

Penicillins and aminoglycosides

The antibacterial effects of all β-lactam antibiotics are **synergistic** with the aminoglycosides. Because penicillin inhibits cell wall synthesis and facilitate the entry of aminoglycosides to inside the bacterial cell.

*[**Note:** these drugs should never be combined in the same infusion fluid because the **basic** aminoglycosides form inactive complex with the **acidic** penicillin]*

Therapeutic uses:

The role for aminoglycosides has decreased substantially due to their **narrow spectrum** and **potential toxicity**.

- Streptomycin is currently used only for **plague**, **brucellosis** and it is one of the 1st line drugs for **TB**.
- Gentamicin and tobramycin are used in the treatment of **gram-negative infections** e.g. urinary tract and respiratory infections.
- They are used in **gram-negative septicemia,** usually combined with penicillin and/or metronidazole.
- **Pseudomonas infections**: they are more efficient when combined with antipseudomonal penicillin
- A combination of vancomycin and gentamicin is useful in the treatment of **enterococcal endocarditis**.
- Neomycin is used **orally** for **hepatic encephalopathy** to suppress intestinal bacteria that produce ammonia.
- Neomycin is used orally for **sterilization of intestine** before surgery and bacillary dysentery.
- Neomycin and gentamycin are used **topically** for skin and eye infections often in combination with polymixin B or bacitracin.

Adverse effects:

Aminoglycosides have a **narrow therapeutic index;** it may be necessary to monitor serum concentrations and individualize the dose especially in **old age**.

- **Nephrotoxicity:**
  - It is due to accumulation of aminoglycosides in the renal tubular cells.

- It ranges from mild reversible effect to severe irreversible toxicity.
- It is increased by co-administration of other nephrotoxic drugs e.g. cephalosporins.

- **Ototoxicity**:
  - It is due to accumulation of aminoglycosides in the endolymph and perilymph of the inner ear causing damage to the hair cells in the organ of Corti.
  - It may affect the cochlear (auditory) or vestibular functions.
  - Deafness may be irreversible.
  - It is increased by co-administration of other ototoxic drugs e.g. loop diuretics and in old age and with renal diseases.

- **Neuromuscular block:**
  - Often occurs after direct intraperitoneal or intrapleural application of large doses of aminoglycosides leading to skeletal muscle weakness.
  - It is treated by immediate administration of calcium gluconate or neostigmine.

- **Malabsorption:**
  - Occasionally observed following the **oral administration** of streptomycin, neomycin, kanamycin. It is due to binding with bile salts and inhibition of pancreatic lipase leading to steatorrhoea and diarrhoea.

Drug interactions:

- **With antibiotics:**
  - With cephalosporins nephrotoxicity increases.
  - Anti-pseudomonal penicillins, and cephalosporins decrease the antibacterial effect of gentamicin if combined together in th**e same syringe (in-vitro)** because penicillins are acidic and aminoglycosides are alkaline.

- **Skeletal muscle relaxants:**
  - Aminoglycosides increase the effect of non-depolarizing NMB agents (see ANS). It could be reversed by neostigmine and calcium gluconate.
  - Aminoglycosides should be administered with great caution during surgery or in the post-operative period.

- **Anticoagulants:**
  - With oral anticoagulants: oral aminoglycosides impair vitamin K production by intestinal bacteria potentiating the effect of anticoagulants.
  - Heparin precipitate aminoglycosides (**avoid their mixing in the same syringe**).

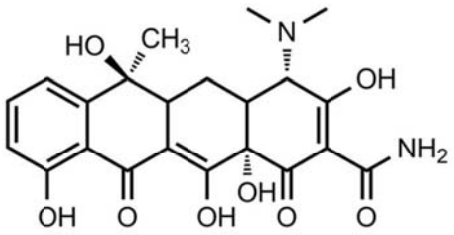
- **Diuretics**: Diuretics e.g. ethacrynic acid, and mannitol potentiate ototoxicity of aminoglycosides.

Tetracyclines

[Oxytetracycline (prototype), doxycycline, tigecycline]

Mechanism of action:

- Tetracyclines bind reversibly to the **30S ribosomal subunit** and **inhibit bacterial protein synthesis.**
- They are bacterio**static**.



Core structure of tetracyclines

Antibacterial spectrum:

Tetracyclines display **broad-spectrum** activity and are effective against:

- Most gram-positive, many gram-negative bacteria and Brucella.
- Rickettsia, Coxiella, Mycoplasma and Chlamydia (intracellular organisms).
- Spirochetes, Actinomycines, Protozoa.
- Helicobacter pylori.

Pharmacokinetics:

- These antibiotics are **partially absorbed** from the stomach and upper gastrointestinal tract and the amounts remaining may alter bacterial flora **leading to super infection**. Because absorption of **doxycycline** is rapid and complete, it has weak effect on intestinal flora.
- Calcium (milk and Ca. antacids), magnesium (Mg hydroxide), aluminum hydroxide and iron interfere with their absorption since they form insoluble chelates with tetracyclines.
- They reach all body fluids and placenta due to its lipid solubility but only **small amounts** can penetrate to CSF (**Doxycycline is the most lipid-soluble**).
- Because of their chelating properties with calcium they tend to be deposited in growing bones and teeth causing yellow discoloration of teeth.
- The primary route of elimination **is renal**. ***Doxycycline* is excreted in stool** and **does not accumulate** in patients with renal impairment.

Therapeutic uses:

- Tetracyclines have broad spectrum activity against both **Gram-positive** and **Gram-negative** organisms, but their use is now declining because of increased resistance and the development of safer drugs.
- Doxycycline is used as **alternative to macrolides** in *Chlamydia, Mycoplasma,* and *Legionella* infections.
- They have broader spectrum than macrolides against **other atypical bacteria** (*Borrelia, Rickettsia, Coxiella)*:

- *Borrelia burgdorferi:* is the cause of **Lyme disease,** a spirochetal infection transmitted by infected ticks. The disease consists of skin rash, fever, and arthritis.
- *Rickettsia:* is a genus of small obligate intracellular bacteria causing **typhus** and **Rocky Mountain spotted fever**.
- *Coxiella burnetii:* is a small obligate intracellular bacterium causing **Q fever.**

The typical "bull's-eye" rash at the site of a tick bite is a common early symptom of Lyme disease

- **Doxycycline** is used orally (100 mg/12h for 3 months) for treatment of **acne vulgaris**.
- **Doxycycline** is effective in treatment of **cholera** (300 mg single oral dose).

Adverse effects:

- **Epigastric distress** (nausea, vomiting, **epigastric burning and hyperacidity**) resulting from irritation of gastric mucosa. This can be prevented by giving tetracycline after meals.
- **Yellow staining** of both the deciduous and permanent teeth and dental enamel hypoplasia (increased susceptibility to caries, as well as retardation of bone growth) because of their chelating properties with calcium. This can occur if tetracyclines are administered after the fourth month of gestation or if they are given to children less than 8 years of age, this is a further **reason for avoiding their use during pregnancy**.

Teeth discoloration caused by tetracyclines

- **Cholestatic hepatitis** particularly in **pregnant** women and at large doses.
- **Phototoxicity:** skin reaction in the form of sunburn, occurs when a patient taking tetracyclines is exposed to sunlight or ultraviolet rays.
- **Superinfection** with resistant *staphylococci* or *C. difficile* (*C. difficile* colitis). Also, decreased synthesis of Vit. B12 leads to sore tongue & black hairy tongue
- **Teratogenesis,** when administered early in pregnancy.

Contraindications:

- Severe hepatic disease and renal disease.
- It should be avoided in patients with peptic ulcer,
- In children (less than 8 years of age)
- In pregnancy and lactation.

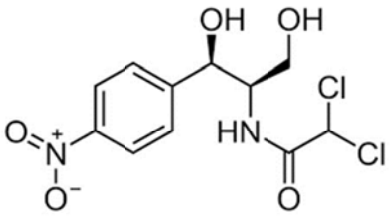
Interactions:

- Avoid simultaneous ingestion of dairy products (milk & cheese), antacids, or iron with tetracyclines because of chelating action of tetracyclines.
- Tetracyclines decrease vitamin K synthesis in intestinal lumen due to inhibition of intestinal flora leading to potentiation of oral anti-coagulant effect.

Chloramphenicol

Mechanism of action:

- Chloramphenicol binds to the **50S ribosomal subunit** and **inhibits bacterial protein synthesis.**
- The drug is either **bacteriostatic** (more common) or bactericidal depending on the organism.



Structure of chloramphenicol

Pharmacokinetics:

- Due to its lipophilic nature, chloramphenicol is **absorbed rapidly**, so there is less alteration of bacterial flora with less susceptibility to superinfection and distributed throughout body fluids.
- Therapeutic levels can penetrate to the CSF and placenta.
- Chloramphenicol is inactivated in the liver by **glucuronyl transferase.**
- Elimination is mainly renal. About 10 % of the administered drug is excreted unchanged (so it is not useful in UTI).

Therapeutic uses:

- Chloramphenicol has broad spectrum against both **Gram-negative and Gram-positive spp.,** but its use is **limited** because of its severe toxicity.
- It could be used as an alternative to macrolides and tetracyclines for diseases caused by **atypical bacteria** *(Mycoplasma, Legionella, Rickettsia, Coxiella, etc).*
- As an alternative to penicillin and cephalosporins for treatment of **meningitis** (due to *H. influenza*), **typhoid fever**, and **anaerobic infections**.
- Used as eye drops (0.5%) for **eye infections**.

Adverse effects:

- **Aplastic anemia** and **bone marrow suppression:**
  - It is dose dependent – rare but fatal.
  - It may occur weeks or months after stopping of the drug.
  - It may be a result of the inhibition of human mitochondrial protein synthesis.
  - Management of BM suppression: see blood.

- **Gray baby syndrome:**
  - It occurs in neonates because their liver cannot metabolize chloramphenicol.
  - It consists of cyanosis, collapse, abdominal distension, and shock.
  - Mortality is high (40%).

Gray baby syndrome

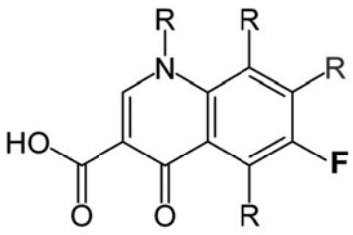
- **Inhibition of cytochrome P-450 enzymes** can increase levels of other drugs.

C. INHIBITORS OF BACTERIAL NUCLEIC ACID SYNTHESIS

Fluoroquinolones

[Ofloxacin, norfloxacin, ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin]

Quinolones are synthetic analogues of Nalidixic acid. The earlier quinolone nalidixic acid did not achieve systemic antibacterial levels and is useful only as urinary antiseptic. Fluorination was found to produce compounds with greater antibacterial activity, achieving useful drug levels in the blood and tissues.



Core structure of fluoroquinolones.
R are variable groups

Members:

- First generation: Nalidixic acid.
- Second generation: Pipemidic acid.
- Third generation: Most are fluorinated. They include **ciprofloxacin, ofloxacin (tarivid), levofloxacin** etc…
- Fourth generation: e.g. **moxifloxacin, trovafloxacin**, they are like third generation with enhanced gram-positive and anaerobes activity.

Mechanism of action:

- They inhibit **type II DNA topoisomerase (DNA gyrase)** that is necessary for bacterial replication.
- Quinolones are **bactericidal**. Like aminoglycosides, they exhibit concentration-dependent killing and a post-antibiotic effect.
- Resistance is due to point mutations in the target enzyme.

Pharmacokinetics:

- The absorption of fluoroquinolonesis is ↓ by stomach contents especially **milk, iron** and **antacids**.

- They reach all body tissues but only **small amounts** can reach CSF.
- Newer fluoroquinolones *(e.g. levofloxacin and moxifloxacin)* accumulate in neutrophils and macrophages, so they have **long $t_{1/2}$** (given once daily) and they are useful against **intracellular organisms.**
- They are excreted primarily **unchanged** in urine, so they are useful in UTIs.

Therapeutic uses:

- Fluoroquinolones are especially indicated in **resistant infections**. Empiric use of these agents in minor infections should be discouraged.
- 3rd generation e.g. Ciprofloxacin have greater activity against **gram-negative bacteria** and moderate activity against **gram-positive organisms and anaerobes.** Newer compounds (moxifloxacin, trovafloxacin) have equal activities against all**.**
- Levofloxacin and moxifloxacin are known as **"respiratory quinolones"** due to their high activity against *S. pneumonia* and other **atypical respiratory pathogens** (*legionella, mycoplasma*).
- 3rdgeneration are used for most **severe systemic infections** e.g. GIT infection, urinary tract infections and prostatitis, respiratory infections, skin and Bone infections (osteomyelitis).
- Treatment of **pseudomonas** infection.
- Ciprofloxacin for **salmonella**; enteric fever

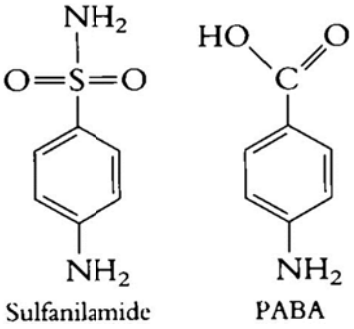
Adverse effects:

- **GIT upset:** nausea, vomiting (the most common).
- **Arthropathy** (in experimental animals):
  - It was manifested as articular damage & erosions in weight-bearing joints.
  - Although this side effect has not been reported in human, the use of fluoroquinolones is **not recommended in children** <18 years.
- **Tendinitis and tendon rupture:** there is increased risk of tendinitis and spontaneous tendon rupture especially with ciprofloxacin. The Achilles tendon is the most frequently affected.
- **CNS (1-2%):** seizures and psychiatric problems. Fluoroquinolones should be used cautiously in patients with **epilepsy**.
- **Prolongation of QT interval** and ↑ risk of torsade de pointes.
- **Inhibition of cytochrome P-450 isozymes** can increase levels of other drugs.

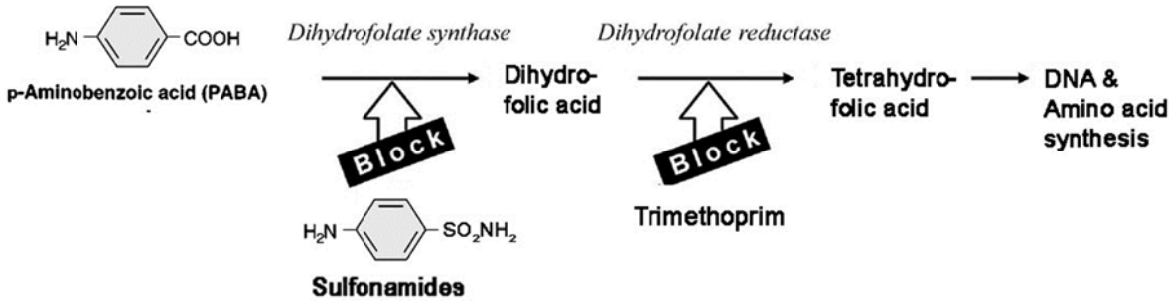
D. INHIBITORS OF BACTERIAL METABOLISM

Sulfonamides and trimethoprim

Mechanism of action:



- Bacteria cannot utilize preformed folic acid; they use *P*-aminobenzoic acid (PABA) as a precursor for synthesis of **dihydrofolic acid** (by the enzyme *dihydrofolate synthase),* then to the active form **tetrahydrofolic acid** (by the enzyme *dihydrofolate reductase),* necessary for bacterial nucleic acid synthesis.
- **Sulfonamides** are structural analogs of PABA. They compete with PABA at the enzyme *dihydrofolate synthase* resulting in inhibition of **dihydrofolic acid** synthesis.
- **Trimethoprim** acts by inhibition of next step (formation of the active form **tetrahydrofolic acid**) via inhibition of *dihydrofolate reductase* enzyme.
- Both sulfonamides and trimethoprim are bacterio**static** drugs.
- **Co-trimoxazole** is a combination of **sulfamethoxazole** (400 mg) and **trimethoprim** (80 mg) to produce **sequential block** of folic acid synthesis.
- Bacterial resistance occurs by development of alternative metabolic pathway for folic acid synthesis.



Pharmacokinetics:

- Most sulfonamides are adequately absorbed from the GIT *(except sulfasalazine)*.
- They reach all body fluids including CSF *(even without meningitis)*.
- Sulfonamides are metabolized in the liver and excreted by the kidney. The acetylated products can precipitate and crystalize in **acidic urine** leading to urinary stones **(crystalluria)**.
- **Alkalinization** of urine can enhance activity of sulfonamides and reduce crystalluria.

Therapeutic uses:

- **Co-trimoxazole:**
  - Treatment of upper respiratory tract infections and bronchitis caused by *S. pneumonia* and *H. influenza.*
  - Treatment of non-complicated **UTIs** and **prostatitis**.
  - The drug of choice for treatment of ***Pneumocystis carinii*** **pneumonia (PCP)** and **toxoplasomosis** in AIDS patients.

- **Other sulfonamide combinations:**
  - **Fansidar** is a combination of sulfadoxine + pyrimethamine is used as an alternative treatment of malaria caused by **chloroquine-resistant *Plasmodium falciparum* malaria**
  - **Sulfasalazine** is poorly absorbed combination of sulfapyridine + 5-aminosalicylic acid used to treat **ulcerative colitis**.
  - **Silver sulfadiazine** is used topically for the treatment of **burn**.

Adverse effects:

- **Hypersensitivity reactions:**
  - Fever and rash are the most common.
  - ***Steven-Johnson syndrome*** is a rare, but fatal form of extensive skin and mucus membrane lesions due to hypersensitivity reaction.

Severe skin reaction and mucocutaneous lesion seen in SJ syndrome

- **Crystalluria:** due to precipitation of sulfonamide metabolites in **acidic** urine leading to colic, hematuria and even anuria.
- **Kernicterus:** sulfonamides cause displacement of bilirubin from plasma protein binding sites. When they are given to **neonates** (or in the last 2 weeks of pregnancy), high free bilirubin levels in the blood can cross BBB and cause permanent brain damage.
- **Anemia:**
  - ***Megaloblastic anemia:*** due to folic acid deficiency (can be prevented by giving folic acid supplementation)
  - ***Aplastic anemia*** leading to granulocytopenia and thrombocytopenia.
  - ***Hemolytic anemia*** in patients with G-6-PD deficiency.

E. MISCELLANEOUS AND LESS COMMON ANTIBACTERIAL AGENTS

Metronidazole

- **Metronidazole** was introduced as an antiprotozoal agent but it is also active against **anaerobic bacteria** such as *Bacteroides*, *Clostridia*, and some *Streptococci* (see antiamebic drugs)
- It is effective in the therapy of **pseudomembranous colitis**, and serious **anaerobic infections** (e.g. sepsis secondary to bowel disease).

Fusidic acid

- **Fusidic acid** is a narrow-spectrum steroid antibiotic active mainly against **Gram-positive bacteria**. It acts by inhibiting bacterial **protein synthesis**.
- It is used in combination with other antistaphylococcal agents in **staphylococcal sepsis**, and **topically** for staphylococcal infections (e.g. as eye drops).
- It is associated with GIT upset (common), skin eruptions and jaundice.

Streptogramins: Quinupristin and dalfopristin

- **Quinupristin** and **dalfopristin** are new class of protein synthesis inhibitors. They inhibit bacterial **protein synthesis** by binding to the 50S ribosomal subunit.
- Individually, they exhibit only mild bacterio**static** activity, but **combined together** as an intravenous injection, they exert **bactericidal** activity against drug-resistant **Gram-positive spp.** including vancomycin-resistant *Enterococci* and MRSA.
- Their use is limited to **serious bacterial infections** when other antibiotics fail.
- Bacterial resistance is still uncommon.
- Both drugs undergo **extensive first-pass** hepatic metabolism and must be given as an **intravenous infusion**.
- **Adverse effects** include inflammation and pain at the infusion site, arthralgia, myalgia and GIT upset.

Oxazolidinones: Linezolid

- **Linezolid** is the first member of this new class of protein synthesis inhibitors (approved in 2000). They inhibit bacterial **protein synthesis** by binding to the **50S** ribosomal subunit.
- It is active against a wide variety of drug-resistant **Gram-positive bacteria** such as vancomycin-resistant *Enterococci* and MRSA. The drug is also effective against some **anaerobes**, such as *C. difficile*.

- Its use is limited to **serious bacterial infections** when other antibiotics fail.
- Bacterial resistance is still uncommon.
- **Adverse effects** include thrombocytopenia and GIT upset.

Rifaximin

- It is a **poorly-absorbed** antibiotic related to rifampicin (see antiTB drugs). It has activity against many Gram positive and Gram negative bacteria. Like rifampin, it inhibits bacterial **DNA and RNA synthesis**.
- It is used **orally** for **hepatic encephalopathy** to suppress intestinal bacteria that produce ammonia.
- It is recently approved to reduce symptoms of abdominal bloating and flatulence associated with **irritable bowel syndrome**.

Nifuroxazide (Antinal)

- It is a **poorly-absorbed** antibiotic related to nitrofurantoin (see UTI). It has activity against many Gram positive and Gram negative enteropathogenic bacteria. The exact mechanism is unclear.
- Bacterial resistance is still uncommon.
- It is used orally as **intestinal antiseptic** in cases of infectious **diarrhea**.

Polymixins

- The polymixin antibiotics are **polymixin B** and **colistin** (polymixin E). They exert their antibacterial action by disrupting the **outer cell membrane**.
- They have selective and rapid bactericidal action on **Gram-negative bacilli**, especially *Pseudomonas* and coliform spp.
- They are **not absorbed** from the GIT.
- Due to their **high toxicity**, they are used only **locally** for eye and skin infections.

Antipseudomonal drugs

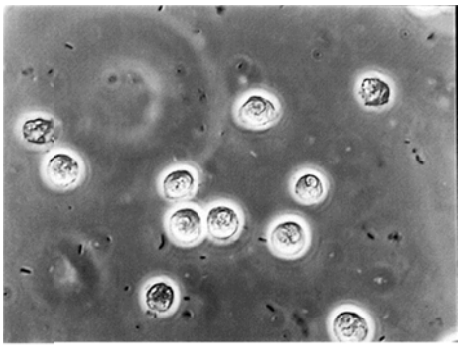
- Antipseudomonal penicillins: e.g. ticarcillin, piperacillin, etc.
- Monobactams: e.g. aztreonam
- Carbapenems: e.g. imipenem, meropenem.
- 3rd and 4th generation cephalosporins: e.g. ceftazidime & cefipime
- Fluorinated quinolones: e.g. ciprofloxacin.
- Tobramycin and gentamycin.

Part 3: CASE STUDY
Treatment of Urinary Tract Infections (UTI)

Definition: infection of the urinary tract indicated by presence of **> 10 pus cells/HPF** in centrifuged urine sample **(pyuria).**

Sterile pyuria: presence of pus cells without organisms. It occurs in some conditions e.g. ***renal TB, analgesic nephropathy, and bladder tumors.***

Bacteriuria: urine culture proves presence of bacteria in urine with or without symptoms of UTI.



Multiple bacilli shown as black and bean-shaped between pus cells in urinary microscopy. These changes are indicative of a UTI.

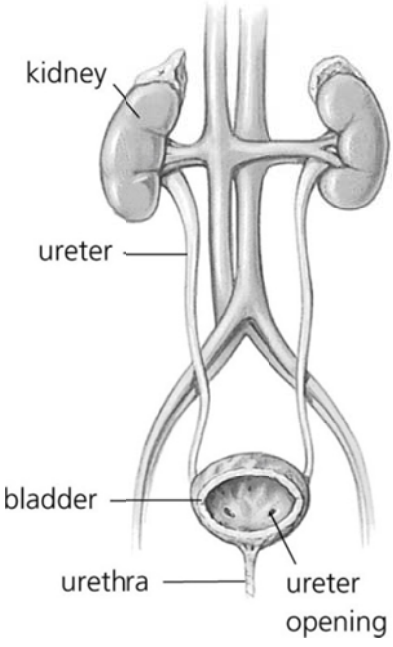
Predisposing factors

- Females > males due to short urethra – Children > adults due to bad hygiene.
- Immunosuppression e.g. in cases of diabetes mellitus.
- Presence of obstruction to urine flow e.g. congenital abnormalities, urethral strictures, and stones.

Causative organisms

- ***E-coli*** is the most **common organism** (80%) in uncomplicated infection.
- *Staphylococcus saprophyticus* (10%).
- Other Gram-negative bacilli e.g. *Proteus, Pseudemonus & Klebsiella* are the commonest organisms. in complicated infection.

Clinical picture



- **Upper UTI (pyelonephritis):** inflammation of the renal tissue or pelvis.
  Manifestations: loin pain, chills, & fever.
- **Lower UTI (cystitis):** inflammation of the bladder & urethra.
  Manifestations: dysuria (burning micturition), urgency & frequency of urination.
- **Uncomplicated (simple) UTI:** occurs for the 1st time without complications. It is usually lower UTI.
- **Complicated (recurrent) UTI:** usually upper UTI with complications e.g. renal stones or anatomical dysfunction.

Laboratory investigations

- **Urine analysis:** the most common test.
  - Macroscopic: color, pH, glucose, protein, etc.
  - Microscopic: WBCs, RBCs, epithelial cells, crystals, casts, ova, etc.
- **Urine culture & sensitivity test:**
  - Culture and sensitivity test is essential in **recurrent UTI** because mixed infection and drug resistance are common.
  - **Does the *in-vitro* test necessarily reflect the *in-vivo* response to drugs? NO because:**
    - The antibacterial drug is **not** excreted in sufficient amount in urine or excreted in urine but as inactive metabolite.
    - Presence of contraindications of the drug e.g pregnancy or children.
  - Most bacteria causing UTI cause alkaline urine, but **strongly alkaline** urine is suggestive of ***Proteus*** infection because it is urease +ve and splits urea into ammonia (NH_3) in the urine.
- **Plain X-ray & i.v. pyelography:** to exclude stone or obstruction**.**
- **Serum creatinine** to avoid use of nephrotoxic drugs.

Management of UTI

1. Specific treatment: Antimicrobial drugs:

- **In lower UTI (usually simple):**
  - The antimicrobial drug should be excreted in large amount in urine.
  - Drugs used routinely: **co-trimoxazole, amoxycillin or nitrofurantoin.**
  - Duration of treatment: **3-5** days.
  - In some cases, simple UTI could be treated by **single** large dose of **fosfomycin** (3g oral once) but with lower cure rates.
- **In upper UTI (usually recurrent):**
  - The antimicrobial drug should be bactericidal of high tissue penetration e.g. **aminoglycosides, fluorinated quinolones or 3rd gen cephalosporins**.
  - Duration of treatment: **10-14** days followed by **chemoprophylaxis** for **15-30** days to prevent recurrence.
  - Indications of chemoprophylaxis: recurrent upper UTI and UTI in pregnancy and children.
  - Drugs used routinely in chemo-prophylaxis: co-trimoxazole, amoxycillin or nitrofurantoin.

2. Changing the urinary pH:

- Normal urine pH is 5.2-6.5. It is possible, by the use of pharmacological agents, to produce urinary pH values ranging from ~ 5.0 to 8.5.

Drug	% Renal excretion of unchanged drug
Ampicillin	75-92
Amoxicillin	60-98
Piperacillin	75-90
Ticarcillin	80-98
Aztreonam	65-95
Imipenem	5-40
Meropenem	62-83
Cephalexin	91-100
Ceftriaxone	65-95
Ciprofloxacin	30-50
Levofloxacin	61-86
Moxifloxacin	20
Gentamycin	>90
Topramycin	>90
Nitrofurantoin	27-56
Co-trimoxazole	50-75

■ Alkalinization of the urine:

Indications:

- To enhance the activity of sulfonamides & aminoglycosides.
- To prevent uric acid stones and sulfonamides crystalluria.
- To relieve dysuria (burning micturition) in some cases of bladder infection.
- *E. coli* is inhibited in alkaline medium.

Alkalinizing agents:

- **Oral:** sodium and potassium citrate salts: citrate is metabolized into bicarbonate which is excreted in urine.
- **Intravenous** bicarbonate solution: contains 5% $NaHCO_3$.

■ Acidification of the urine:

Indications:

- To enhance the activity of nitrofurantoin, fosfomycin, and hexamine.
- Acidifying agents can lead to dangerous systemic acidosis in cases of renal or hepatic impairment.

Acidifying agents:

- **Oral:** ascorbic acid > 2 g/d.
- **Intravenous** ammonium chloride (NH_4Cl) solution.

3. Urinary antiseptics:

■ Hexamine (Methenamine)

- In acidic urine, hexamine is hydrolyzed into ammonia and **formaldehyde**. Formaldehyde is bactericidal and lacks bacterial resistance. Urine must be **acidified** (pH below 5.5) to get this effect.
- **Side effects:** Chemical cystitis.

■ Nitrofurantoin

- Nitrofurantoin causes bacterial **DNA damage** by an unclear mechanism
- It is used **only** as a **urinary antiseptic** in **lower simple UTI** against ***E. coli.*** Other urinary tract Gram-negative bacteria are often resistant.
- It becomes more active in **acidic** urine.
- It is **contraindicated** in renal failure.
- **Adverse effects** include hemolytic anemia in patients with G-6-PD deficiency, peripheral neuritis, and dark brown urine.

■ Fosfomycin

- Fosfomycin inhibits bacterial **cell wall** synthesis.
- It is a **broad spectrum** antibiotic against many **Gram positive** and **negative** spp.
- It is used **only** as a **urinary antiseptic** in **lower simple UTI**.
- It becomes more active in **acidic** urine.

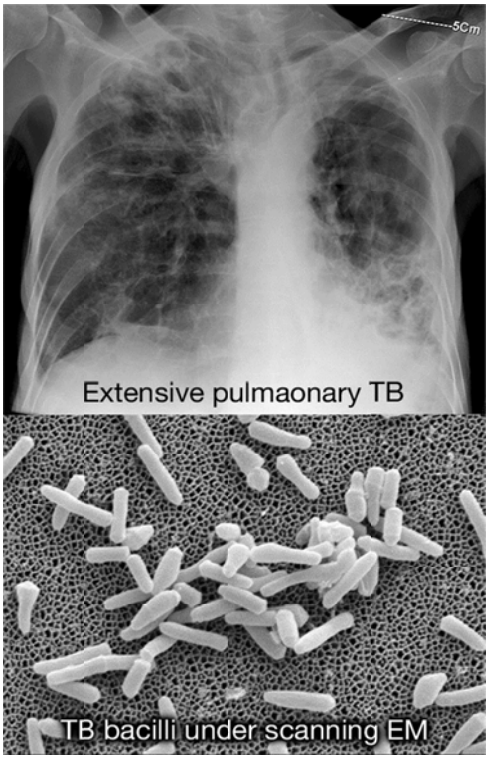
Causes of failure of treatment:

- Improper choice, dose, or duration of drug treatment.
- Bacterial resistance.
- Presence of complications e.g. renal calculi, ureteric stricture, etc.
- Renal failure.
- Immunocompromized patient: e.g. DM

	Contraindicated drugs	Recommended drugs
UTI with Renal Failure	▪ Nitrofurantoin: absolutely contraindicated because it is nephrotoxic and needs acidic urine to act while we cannot acidify urine in renal failure. ▪ K salts and acidifying agents: absolutely contraindicated because they can cause dangerous acidosis or hyperkalemia. ▪ Aminoglycosides.	▪ Penicillin ▪ Most cephalosporins ▪ Co-trimoxazole
UTI in Pregnancy and lactation	▪ Sulfonamides → kernicterus. ▪ Fluorinated quinolones → arthropathy. ▪ Aminoglycosides → congenital deafness. ▪ Tetracyclines → teratogenic and cause yellow staining of teeth. ▪ Chloramphenicol → grey baby syndrome.	▪ Penicillin ▪ Most cephalosporins

Part 4: Chemotherapy of TB and Leprosy

Overview:



- *Mycobacterium tuberculosis*, one of a number of mycobacteria, can lead to serious infections of the lungs, genito-urinary tract, skeleton, and meninges.
- Worldwide estimations record 9 million new cases every year, and approximately 2 million die of the disease each year.
- Treatment of TB (and other mycobacteria) presents therapeutic problems because:
- Tubercle bacilli are either extracellular (metabolically active), intracellular (metabolically inactive) or inactive inside necrotic caseous material. However, most of tubercle bacilli are intracellular with slow growth rate. Resistant strains occur naturally to any agent given as sole drug.
- Bacterial **resistance** is common, particularly in patients non-adherent to the treatment protocol.
- The organism grows slowly and may require 6-24 months of treatment.

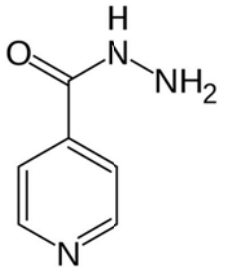
General rules during TB therapy:

- **Never treat TB by a single drug:** at least two of the first line drugs, are used to prevent emergence of resistant strains.
- **Never add a single drug to a failing regimen!**
- Treatment must be continued for long period (6-24 months) to eradicate bacilli.
- **Poor patient compliance** is the commonest cause of therapeutic failure, so it is better to give drugs in a single daily dose to enhance patient compliance.
- The patient must be **followed up** for detection of adverse effects of drugs and/or therapeutic failure.

FIRST LINE ANTI-TUBERCULOUS DRUGS

- **Isoniazide**
- **Rifampicin (Rifampin)**
- **Ethambutol**
- **Pyrazinamide**
- **Streptomycin**

1. Isoniazid (INH)



Mechanism of action

- INH is an analog of pyridoxine (vitamin B6).
- INH is a **prodrug** that is activated inside *M. tuberculosis* into active metabolite which inhibits the synthesis of **mycolic acid**, an essential component of the **mycobacterial cell wall (bactericidal).**
- **Mycolic acid** is present only in *M. tuberculosis,* so INH has **no activity** on other bacteria or atypical mycobacteria.
- **Resistance** is due to mutations in the enzyme responsible for conversion of INH into the active metabolite.

Pharmacokinetics

- Absorption of INH is good after oral administration. It penetrates most body fluids including the CSF.
- It accumulates in caseated lesions and can attack both extra- and intracellular bacilli.
- INH is acetylated in the liver. The rate of acetylation is genetically determined ("rapid acetylators" and "slow acetylators").

N.B.

INH exerts **competitive antagonism with pyridoxine** for enzyme apotryptophan leading to clinical picture of pyridoxine deficiency (neurotoxicity).

Therapeutic uses

- **Treatment of TB:** INH is **administered in combination** with one or more other first-line drugs to minimize the development of resistance.
- For **prophylaxis** (close contacts), INH is used alone.

Adverse effects

I **Inhibition** of CYP450 (↓ metabolism of other drugs, especially phenytoin).

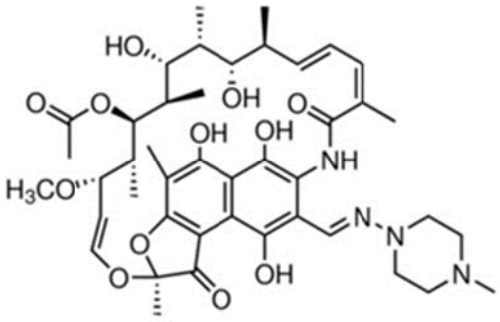
N **Neurotoxicity:**
- High levels of INH compete with pyridoxine at the enzyme *pyridoxal kinase* leading to **peripheral neuropathy**.
- It is more common in **slow acetylators**.
- It could be minimized by co-administration of **pyridoxine** (vitamin B6).

H **Hepatotoxicity** with jaundice (3%)**:**
- It is due to accumulation of toxic metabolites in the liver.
- It is more common in **rapid acetylators** and in individuals over 35 years.

H **Hypersensitivity reactions** with rash and fever (2%).

H **Hemolytic anemia** in patients with G-6PD deficiency

2. Rifampin (Rifampicin)



Mechanism of action

- Rifampin selectively inhibits bacterial **DNA-dependent RNA polymerase enzyme** leading to ↓ RNA synthesis (human enzyme is not affected).
- Rifampin is **bactericidal** for both intra- and extracellular *M. tuberculosis*, and atypical mycobacteria.
- It is also effective against many **Gram-positive** and **Gram-negative** bacteria.
- **Resistance** develops rapidly if the drug is used **alone**. It is due to a change in the polymerase enzyme.

Pharmacokinetics

- Rifampin is absorbed orally and can reach all body tissue and fluids including the CSF, pleural and ascetic fluids.
- It can reach TB cavities, sputum and penetrate macrophage killing intra- and extracellular TB bacilli.
- It enters **enterohepatic circulation** and **induces** hepatic microsomes to **decrease the half-lives** of other drugs.
- It is excreted through the bile and urine. Its metabolites cause ***orange-red*** discoloration of urine, stool, tears, and sweat; the patient should be **warned**.

Therapeutic uses

- Treatment of **TB** in combination with ***INH*** and ***pyrazinamide***. Rifampin and INH are the most effective antituberculous drugs.
- Although rifampin has activity against many Gram positive and negative bacteria but should be used **only against TB** to prevent development of resistance.
- Treatment of **leprosy** in combination of ***dapsone*** and ***clofazemine***.
- Used **prophylactically** for individuals exposed to **meningitis** caused by *Meningococci* or *H. influenzae*.

Adverse effects

- **Hepatotoxicity (rare):** abnormal liver enzymes, jaundice, etc. especially in old patients and patients with chronic liver disease.
- **Microsomal enzyme induction** leading to decrease half-lives of other drugs.
- **Flu-like symptoms:** with intermittent therapy.
- **Red tears and urine:** harmless, but can stain contact lenses.
- **GIT** upset (nausea and vomiting) and skin **rash**.

3. Ethambutol

Mechanism of action

- Ethambutol inhibits ***arabinosyl transferase*** involved in **cell wall** biosynthesis.
- Ethambutol is specific bacterio**static** for *M. tuberculosis.* It is active against intra- and extracellular TB bacilli.
- Relatively **less toxic** and resistant strains develop **slowly**.

Therapeutic uses

- Treatment of TB in combination with INH and rifampin to minimize **resistance**.
- Treatment of **TB during pregnancy** because it is **the least toxic**.

Adverse effects

- **Peripheral neuropathy and visual disturbances (1-5%)**:
  - Optic neuropathy manifested by field defects and red-green color blindness. These effects are reversible on stopping the drug.
  - There is no specific treatment other than stopping of the drug.
- **Hyperuricemia** and **gout**: due to ↓ uric acid excretion.
- **GIT disturbance** & hypersensitivity reactions.

4. Pyrazinamide

Mechanism of action

Pyrazinamide is taken up by the macrophages and is converted into the active product by the **acidic** medium of the lysosomes inside the macrophages. It inhibits mycobacterial **cell wall** functions.

Therapeutic uses: In combination with INH and rifampin to minimize resistance

Adverse effects

- **Hepatotoxicity** is the major side effect.
- **Hyperuricemia** and **gout**: due to ↓ uric acid excretion.

5. Streptomycin

- It is one of the aminoglycosides. It is bacteri**cidal** for **extracellular** bacilli but it is ineffective against intracellular bacilli. Why?
- **Therapeutic uses:** in combination with INH & rifampin to treat **resistant**

pulmonary TB and **renal TB** (because 50-90% is excreted unchanged via the kidney). It is given by IM injections.

- **Adverse effects:** nephrotoxicity, ototoxicity (8th nerve damage), and NM block.

SECOND-LINE ANTI-TUBERCULOUS DRUGS

- **Para aminosalicylic acid**
- **Ethionamide**
- **Cycloserine**
- **Fluoroquinolones**
- **Capreomycin**

1. Para aminosalicylic acid (PAS)

PAS is an analog of PABA; it works similar to sulfonamides but only against mycobacteria.

2. Ethionamide

Ethionamide, like isoniazid, blocks the **synthesis of mycolic acids.** Resistance develops rapidly. It commonly produces severe GI disturbances.

3. Other drugs: fluoroquinolones, cycloserine, etc.

REGIMEN OF TB THERAPY

- **Patients with active TB:**
  - **Initial phase (first 2-4 months)**: **4 drugs** are used **(RIPE)**: (**Rifampin + INH + Pyrazinamide + Ethmabutol**). ***N.B.*** *Recent guidelines now recommend giving a 'fourth drug' such as Ethambutol routinely - previously this was only added if drug-resistance was suspected.*
  - **Continuation phase (next 4-6 months):** at least **2 drugs** are used (**INH + rifampin**).

- **Patients with latent TB** *(i.e. patients with +ve Tuberculin skin test and had history of contact to a person proved to have TB):* **INH** alone for 6 months or dual Rifampicin + INH for 3 months.

- **Patients with meningeal TB:** are treated for a prolonged period (12-18 months) with the addition of **steroids.**

- **TB during pregnancy:** the only anti-TB drug which is absolutely contraindicated is streptomycin because of the high risk of congenital deafness. The other first line anti-TB drugs are safe for use in pregnancy.

- **TB with liver disease:** INH, rifampin, and pyrazinamide are hepatotoxic but because of their effectiveness, they should be used depending on monitoring of liver function tests. In severe liver damage, only one drug can be used.

CHEMOTHERAPY OF LEPROSY

1. Dapson

- Structural analogue of PABA and chemically related to sulfonamides.
- **Mechanism of action:** similar to sulfonamides (bacteriostatic).
- **Therapeutic uses:** treatment of leprosy with rifampin for 2-5 years.
- **Adverse effects:**
  - Nausea, vomiting, skin rash
  - Hemolysis and methemoglobinemia,
  - Exacerbation of skin lesion of lepromatous leprosy.

2. Clofazimine

- **Mechanism of action:** inhibit mycobacteria DNA synthesis (bactericidal).
- **Therapeutic uses:** in combination with dapson and rifampin to prevent resistance.
- **Adverse effects:** abdominal pain, brown urine, atropine-like actions.

3. Rifampin: is the most active antilepromatous drug available.

Part 5: Antiviral Drugs

ANTI-HERPES VIRUS AGENTS

1. Acyclovir

- **Acyclovir** is a purine analog that **inhibits the activity of viral DNA polymerase.**
- It is active against **herpes simplex virus (HSV)** types I and II, and to a lesser extent against **Epstein–Barr virus, varicella-zoster virus,** and **cytomegalo virus** (**CMV).**
- **Adverse effects:** reversible nephrotoxicity and neurotoxicity

2. Gancyclovir

- Similar to acyclovir but highly active against **CMV.**
- **Adverse effects:** reversible neutropenia and thrombocytopenia

ANTI-INFLUENZA AGENTS

1. Amantadine and rimantadine

- Amantadine and rimantadine inhibit the **uncoating** and replication of the viral RNA in infected cells.
- They are used to treat **influenza A** infections when administered within the first **48 hours** of symptoms, and as prophylaxis during flu season.
- **Adverse effects:** mild CNS effects (insomnia, nervousness) and some GI dysfunction. Patients with a history of **seizures** require close monitoring.

2. Ribavirin

- Ribavirin, a guanosine analog that appears to inhibit viral RNA polymerases; the mechanism of action is **not clear.**
- It is used to treat **respiratory syncytial virus (RSV)** and **influenza A and B**.
- **Adverse effects:** Hemolytic anemia and teratogenic in pregnancy.

3. Zanamivir and Oseltamivir (Tamiflu)

- Zanamivir, (administered by inhalation), and oseltamivir, (administered orally), are **neuraminidase inhibitors.**
- They are used for the treatment and prophylaxis of **acute uncomplicated influenza** infection. The agents are effective against both influenza A and B.
- Abdominal pain and **GI dysfunction** are common with oseltamivir. Zanamivir may cause **bronchospasm**.

ANTI-RETROVIRAL DRUGS

1. Reverse Transcriptase Inhibitors (RTIs):

- **Nucleoside analogs (NRTI):** zidovudine, lamivudine, tenofovir
- **Non-Nucleoside analogs (NNRTI):** efavirenz, nevirapine

Adverse effects:

- All agents: peripheral neuropathy and interaction with CYP450.
- Zidoviodine: myopathy and anemia.

2. Protease inhibitors: ritonavir, lopinavir, atazanavir

Adverse effects:

- All agents: diabetes, hypertriglyceridaemia and hypercholesterolaemia
- Ritonavir is the most potent inhibitor of CYP450 known.

3. Fusion receptor protein inhibitors: Enfuvirtide.

- It competes with the **gp41 subunit** of the HIV-1 viral envelope and prevents fusion to the cell membrane CD4 receptors.

4. Integrase inhibitors: Raltegravir

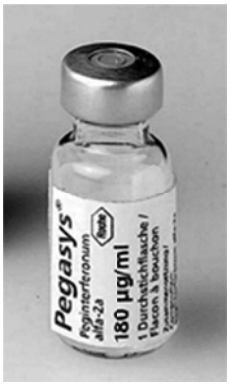
- It is a **new class** of drugs that inhibit the viral enzyme **integrase** to prevent HIV replication and viral integration into the host cell.

ANTI-HEPATITIS VIRUS DRUGS

1. Interferon-alpha and peginterferon-alpha (Pegasys)

- Interferons are group of natural cytokines released by host cells in response to infection. They have several classes; all have antiviral effects and regulate the immune function.
- Genetically engineered interferon-α is used, in combination with **ribavirin**, for both **HBV** and **HCV**. Peginterferon has long duration (injected **once-weekly s.c.).**

- **Antiviral mechanism:**
  - Interferon binds to cell membrane receptors to initiate a series of reactions leading to inhibition of viral replication.
  - They promote apoptosis of viral-infected cells.



- **Adverse effects:**
  - Flu-like symptoms: muscle pain, fever, and **fatigue**.
  - Bone marrow depression: neutropenia.
  - Neuropsychiatric effects: depression, convulsions.

2. Lamivudine

- It is a nucleoside reverse transcriptase inhibitor (NRTI) used for **HBV infections**, providing effective and rapid response in most patients, and slows progression of liver fibrosis.

3. Sofosbuvir (Sovaldi®)

- It is a nucleotide analog used for treatment of **HCV** in combination with ribavirin and interferon.
- It works by inhibition of **viral RNA polymerase**.

4. Grazoprevir/Elbasvir (Zepatier®)

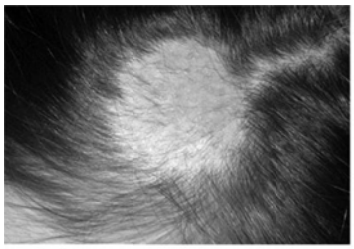
- It is a recently approved combination for treatment of **HCV** (genotypes 1, 3, 4).
- **Grazoprevir** is a NS3/4A protease inhibitor. This protease enzyme enables the C virus to survive and replicate in host cells. **Elbasvir** is a NS5A inhibitor. NS5A is a protein needed by the virus for various stages of infection.
- The effectiveness and adverse effects of sofosbuvir, grazoprevir, and elbasvir are under current investigation.

Management of chronic HCV infection

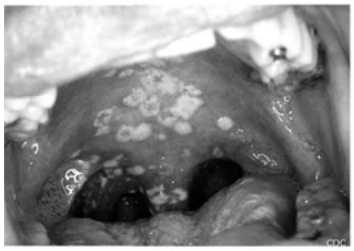
- Treatment with interferon-α **alone** gives 10-15% success rate in achieving long term clearing of plasma hepatitis C RNA. A combination of **interferon and ribavirin** gives 50% success rate.
- About 50% of successfully treated patients will **relapse** despite treatment.
- **HCV genotype** will give guidance to the **length of treatment** and **response rate**:
  - Those with genotype **2** and **3** can achieve SVR after **24** weeks as they have better response to treatment.
  - In genotype **1** and **4**, therapy is continued for **48** weeks due to **lower** response rate.
- The following also predict **a good long term response to interferon:**
  - Younger age.
  - Female gender.
  - Absence of cirrhosis on liver biopsy.
  - Non-black racial origin.
  - Low hepatic iron.
- **No HCV vaccine** is currently available.

Part 6: Chemotherapy of Fungal Infections

Fungal infection is termed **mycosis**


Ringworm of the scalp

Onychomycosis of nail


Oropharyngeal candidiasis

Tinea of the face

Types of fungal infections:

- **Mucocutaneous (superficial) infections:**
  - Dermatophytes: cause infection of **skin**, **hair**, and **nails**: e.g. tinea capitis (scalp), tinea cruris (groin), tinea pedis (foot), onychomycosis (nails).
  - Yeasts: cause infections of moist skin and mucous membranes: e.g. ***Candida albicans*** causing oral, pharyngeal, vaginal, & bladder infections.
- **Systemic mycoses:** are fungal infections affecting internal organs. It occurs in immunocompromized patients e.g. cryptococcosis, and aspergillosis (lung).

Classification of antifungal drugs:

A. Drugs for mucocutaneous infections:	**Systemic drugs**	▪ **Azoles:** Fluconazole, Itraconazole, Voriconazole. ▪ Griseofulvin ▪ Terbinafine
	Topical drugs	▪ **Azoles:** Ketoconazole, Miconazole, Clotrimazole, Tioconazole, etc. ▪ Nystatin ▪ Terbinafine. ▪ Other drugs: Tolnaftate, Ciclopirox, Naftifine, Whitfield ointment, Gentian violet, Castellani paint, Tincture iodine.
B. Drugs for systemic infections:		▪ **Azoles:** Fluconazole, Itraconazole, Voriconazole. ▪ Amphotericin-B ▪ Flucytosine ▪ Caspofungin

1. Azoles

[Ketoconazole, Miconazole, Fluconazole, Itraconazole, Voriconazole]

Mechanism of action

- Azoles inhibit fungal **cytochrome P450** necessary for **ergosterol synthesis**, a major component of fungal cell membrane. This will alter membrane permeability and disrupt its function.
- They are **broad spectrum** fungistatic against many **dermatophytes and candida.**

Pharmacokinetics

- Absorption of azoles from stomach if affected by food and gastric HCl.
- Fluconazole can reach the CSF with good concentrations. The other drugs cannot.
- Fluconazole is excreted in the urine mostly unchanged

Therapeutic uses

- **Superficial fungal infections: [ketoconazole – itraconazole – miconazole]**
  - Dermatophytes infection of the **skin** (tinea), **hair**, and **nails** (onychomycosis):
    - For **skin** infection: treatment continued for **2-4** weeks.
    - For **hair** infection: treatment continued for **6-8** weeks.
    - For **nail** infection: treatment continued for **3-6** months.
  - Mucocautaneous candidiasis: oropharyngeal, vulvovaginal, etc.
- **Systemic fungal infections: [itraconazole – fluconazole – voriconazole]**
  - **Itraconazole** (orally or IV) is the drug of choice for systemic ***blastomycosis***.
  - **Fluconazole** (orally or IV) is the drug of choice for systemic candidiasis, and ***cryptococcal meningitis*** (because it the only azole that can cross to CSF with good concentration).
  - **Voriconazole** is the drug of choice for ***invasive aspergillosis*** of the lung.

Skin lesions of blastomycosis

N.B. Itraconazole has largely replaced ketoconazole in most uses.

Adverse effects

- **Hepatotoxicity** and ↑ of serum transaminases.
- **Azoles inhibit hepatic CYP450 enzymes** (fluconazole is the least among them).
- **Ketoconazole** causes **antianderogenic effects:** gynecomastia and impotence due to ↓ gonadal steroid synthesis.
- **Voriconazole** causes **transient visual disturbances.**

2. Amphotericin-B

Mechanism of action

Amphotericin B is polyene macrolide that binds to ergosterol of fungal cell membranes and forms **"pores"** that alter membrane stability and allow **leakage of cellular contents.**

Pharmacokinetics

- Amphotericin B is **polar** compound that **cannot be absorbed** from the GIT or cross the CSF. It should be administered **IV** or intrathecal.
- Half-life is **15 days**. Dialysis is **ineffective** in case of toxicity.
- Because of significant toxicity, amphotericin B is available in **liposomal form** in which the drug is enclosed in lipid microspheres **"liposomes"**. These lipid microspheres bind preferentially to ergosterol in the fungal cell membrane with lower affinity to mammalian cell membranes.

Therapeutic uses

Amphotericin B has the **broadest spectrum** of activity. It is used to treat **severe systemic fungal infections**, including those caused by *Candida albicans, Histoplasma capsulatum, Cryptococcus neoformans, Coccidioides immitis, Blastomyces dermatitidis, Aspergillus spp., and Sporothrix schenckii.*

Adverse effects

- Amphotericin B is highly **toxic** drug. It causes **nephrotoxicity** in 80% of patients which is dose-dependent and may be irreversible.
- **Chills** and **fever** in 50% of patients.
- Seizures and neurotoxicity
- Hypokalemia and thrombocytopenia

OTHER ANTIFUNGAL DRUGS

Flucytosine

- Flucytosine is actively transported into fungal cells and is converted to the uracil form **5-fluorouracil (5-FU)** which inhibits **nucleic acid synthesis.** Human cells lack the ability to convert large amounts of flucytosine into 5-FU.
- It is often used in **combination with other antifungal agents** (because of rapid development of resistance) to treat **severe systemic** fungal infections.
- **Adverse effects:** Flucytosine is relatively nontoxic; the major adverse effect is **depression of bone marrow** at high doses and **hair loss**.

Griseofulvin

- Griseofulvin binds to **microtubules** and prevents **spindle formation and mitosis in fungi.** It is fungi**static** and requires long duration of therapy.
- The drug binds to keratin structures and **accumulates in skin, hair, and nails.**
- Griseofulvin is used orally for long-term therapy of **dermatophyte infections of the hair and nail.**
- **Adverse effects: hepatotoxicity** (liver functions should be checked during therapy), hypersensitivity reactions (skin rash), and CNS effects.

Terbinafine

- Terbenafine inhibits the fungal enzyme ***squalene epoxidase***. This leads to the accumulation of the sterol squalene, which is toxic to the organism.
- Like griseofulvin, it accumulates in keratin structures and used orally or topically for treatment of **dermatophyte infections of the hair and nail.**

Nystain

- Nystatin is polyene macrolide very similar in kinetics and mechanism to amphotericin B.
- It is **too toxic** for parenteral administration and is used only topically.
- It is active mainly against **Candida,** and is used topically for oralpharyngeal and vaginal candidiasis.

Caspofungin

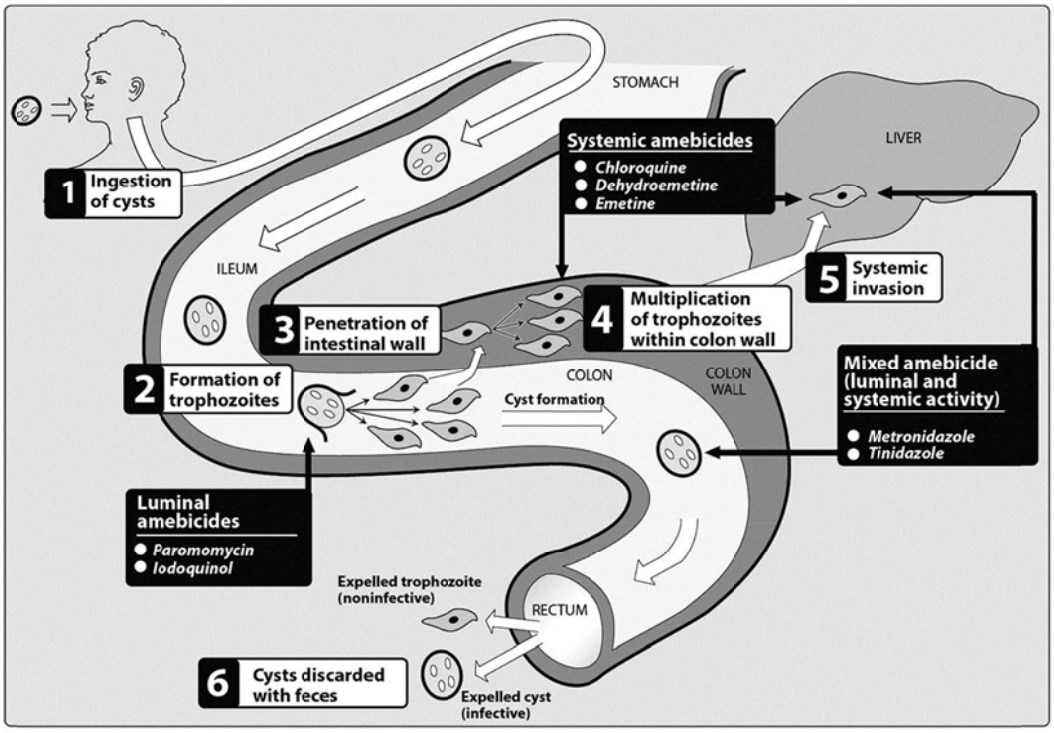
- It is large cyclic peptide that **disrupts the fungal cell wall** resulting in cell death.
- **Caspofungin** is used by i.v. route for salvage therapy in patients with **severe invasive aspergillosis** or **esophageal candidiasis** who failed to respond to amphotericin B (second line drug).

Ciclopirox

- Broad-spectrum antifungal effective against **dermatophytes and yeasts**. The mechanism is **unclear.**
- It is used topically for skin and nail infections.

Part 7: Antiamoebic Drugs

- The causative organism for amoebiasis is ***Entamoeba histolytica***. Initial infection occurs by ingestion of the **cyst** form. The infectious cysts pass into the colon, where they develop into **trophozoites**. These motile organisms adhere to colonic epithelial cells. Here, the trophozoites feed, multiply, encyst and eventually pass out in the feces **"asymptomatic carrier"**.
- The motile organism invades the colonic mucosa causing **"amoebic dysentery"**. They may also spread to the liver causing acute **"amoebic liver abscess"**.



Classification of antiamoebic drugs:

A. Luminal amoebicidal drugs: these agents destroy the trophozoites of *E. histolytica* that eventually form into cysts in the intestine.	▪ **Diloxanide** ▪ **Iodoquinol** ▪ **Paromomycin**
B. Tissue amoebicidal drugs: they destroy the invading **trophozoite** in the tissues (e.g. liver) but are ineffective against the trophozoites in the intestinal lumen. **Their use now is very limited.**	▪ **Emetine and dehydroemetine** ▪ **Chloroquine:** active only against liver infection.
C. Mixed tissue and luminal amoebicides:	**Metronidazole, tinidazole, ornidazole.**

1. Mixed amebicides: Metronidazole

Structure and mechanism of action

- Metronidazole is 5-nitroimidazole compound. Anaerobic protozoa & bacteria lack mitochondria; instead, they have *ferredoxin oxidoreductase enzyme* in the cytoplasm to generate ATP.
- This enzyme system can transfer electron to the 5-nitro groups of metronidazole converting it into **cytotoxic product**. This product causes DNA damage and inhibits DNA repair.
- Metronidazole is active against **anaerobic organisms** including *anaerobic bacteria: (e.g. Bacteroids, C. difficile), E. histolytica, G. lamblia, T. vaginalis, B. coli.*

Therapeutic uses

- **Amebiasis:** Metronidazole is the most effective agent available for the treatment of all forms of amoebiasis except asymptomatic person that excrete cysts. Metronidazole kills trophozoites but not cysts.
- **Urogenital trichomoniasis:** 250 mg t.d.s. for 7 days is the treatment of choice. The other partner should be treated simultaneously.
- **Giardiasis:** 250 mg t.d.s. for 5 days.
- **Balantidiasis:** 750 mg t.d.s. for 5 days
- **Severe anaerobic infections:** e.g. puerperal sepsis, peritonitis, acute ulcerative gingivitis, etc.

Adverse effects

- **GIT:** nausea, vomiting & metallic taste.
- **CNS:** insomnia, headache, vertigo, parasthesia, ataxia, & seizures.
- **Blood:** bone marrow depression, leukopenia & thrombocytopenia.
- **Disulfiram-like reaction:** metronidazole causes accumulation of acetaldehyde if alcohol is consumed leading to nausea & vomiting.
- **Dark brown urine.**

N.B. Disulfiram is a drug used for treatment of chronic alcoholism. It blocks metabolism of acetaldehyde by the enzyme *aldhyde dehydrogenase* leading to accumulation of acetaldehyde → nausea, vomiting, flushing, etc.

2. Luminal amebicidal drugs:

- **Diloxanide:** Is active against both trophozoite and cyst forms in the intestinal lumen but **not** in the intestinal wall or extraintestinal tissues. The mechanism is **unknown**.

- **Iodoquqinol:** it is iodinated quinolone derivative. Is active against both trophozoite and cyst forms in the intestinal lumen but **not** in the intestinal wall or extraintestinal tissues. The mechanism is **unknown**.

  Because it contains iodine, it can cause **dermatitis** and **persistent diarrhea** (iodine intolerance).

- **Paromomycin:** it is a poorly-absorbable aminoglycoside antibiotic. It is used as alternative to iodoquinol and diloxanide. The antiamoebic mechanism is **unclear** but may be due to alteration of the cell membrane permeability and leakage of cell contents.

Uses of luminal drugs

- They are used for treatment of asymptomatic or mild intestinal infection.
- They can also be added to metronidazole in acute amoebic dysentery as well as hepatic abscess to eradicate cysts in the lumen which may cause relapse.

3. Tissue amebicidal drugs:

- **Emetine and dehydroemetine:** Emetine is a plant alkaloid. Dehydroemetine is a potent derivative. All have significant toxicity.
- **Chloroquine:** it is a synthetic drug (see treatment of malaria).
- Both drugs can be used as alternative to metronidazole in the treatment of **amoebic liver abscess** or extraintestinal amoebiasis, however, their use now is **very limited**.

CT scan showing amebic liver abcess

Part 8: Antimalarial Drugs

Life cycle of malaria and sites of drug actions

A. Sexual cycle in the female mosquito.

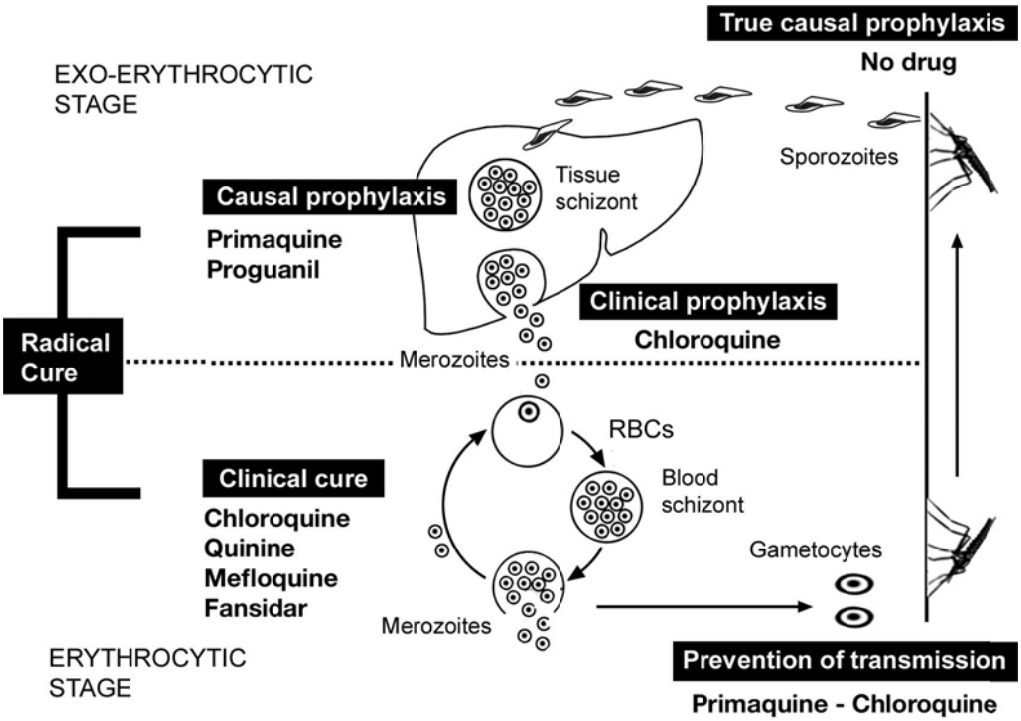
B. Asexual cycle in man and consists of:

- **Sporozoite stage:** sporozoites injected by the mosquito rapidly enter the liver.
- **Exo-erythrocytic (liver) stages:**

  Pre-exo-erythrocytic stage (primary liver stage):
  Sporozoites in the liver undergo multiplication to form **tissue schizont** which eventually ruptures and releases **merozoites** to infect RBCs. During this stage the patient is asymptomatic.

  Secondary exo-erythrocytic stage (persistent liver stage):
  Sporozoite of *P. vivax* or *P. ovale* form dormant **hypnozoites** in the liver that can persist and reactivated after a latent period causing relapse of malaria.

- **Erythrocytic stage:** merozoites liberated from ruptured liver schizont will invade RBCs to form **blood schizont**. This blood schizont will eventually rupture to liberate merozoites and toxic products causing fever and clinical manifestations of malaria (every 3rd day in tertiary malaria).
- **Gametocytes stage: s**ome merozoites develop into gametocytes which will be sucked by the mosquito to complete the sexual cycle.



Types of treatment:

I. Chemoprophylaxis: (Killing the parasite before multiplication inside RBCs)

- **Causal prophylaxis:** killing the parasite in the liver:
  Proguanil and primaquine.
- **Clinical prophylaxis:** killing the parasite as soon as they reach the RBCs:
  Proguanil and chloroquine.

II. Suppressive or clinical cure: (killing the parasite in the RBCs)

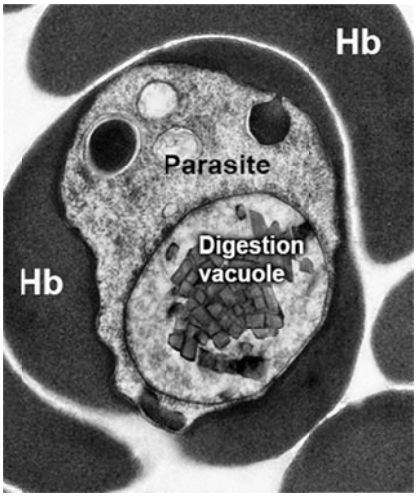
- Chloroquine: for chloroquine-sensitive malaria.
- Quinine and mefloquine: for chloroquine-resistant malaria.
- Artemisinin and its analogs: for chloroquine-resistant malaria.
- Sulfonamides and pyrimethamine: Fansidar (sulfadoxine + pyrimethamine).

III. Radical cure: (clearing the dormant hypnozoite from the liver to prevent relapse)
Primaquine + chloroquine

IV. Prevention of transmission: (killing the gametocytes)
Proguanil, primaquine, and pyrimethamine.

Chloroquine

Mechanism of action



- Inside RBCs, the malarial parasite digest hemoglobin in a vacuole inside the parasite cell to acquire amino acids essential for multiplication.
- Chloroquine enters the digestion vacuole by simple diffusion. The acidic pH inside the vacuole makes chloroquine **ionized** and, thus, cannot diffuse outside the vacuole and becomes trapped inside it.
- Inside the vacuole, the ionized chloroquine reacts with the digestive products of **heme** molecule and forms a **highly toxic complex** that kills the parasite.
- Chloroquine is a **blood schizonticide** for *Plasmodium vivax, P. ovale, and P. malariae* but **not** for *P. falciparum* which is usually resistant.

Pharmacokinetics

- Absorption from the GIT is good and complete.
- It binds to melanin-rich tissue e.g. skin, eye, etc.
- Chloroquine has **very high Vd** (100-1000L/Kg) and slow rate of elimination.

Therapeutic uses

- **Malaria** (except *P. falciparum*):
  - For treatment of acute attack: 1g IV followed by 500 mg after 6, 24, 48h.
  - For chemoprophylaxis: 500 mg once/week orally.
- As a 2nd line for treatment of **amoebic liver abscess:** 500 mg daily for 14 days.
- As a 2nd line (after metronidazole) for treatment of **giardiasis.**
- Treatment of **rheumatoid arthritis** and **SLE**: 500 mg/day then 250 mg/day.

Adverse effects

- **Long term administration:**
  - **Skin:** pruritus (common), dermatitis, bleaching of hair, and alopecia.
  - **Visual disturbances**: corneal deposits, optic atrophy, and retinopathy.
- **Rapid i.v. injection** causes hypotension, ECG changes, and **cardiac arrest**. Parenteral administration is better avoided or should be infused **slowly.**
- **Hemolysis** in G-6PD deficient persons.

Quinine (and Quinidine)

Structure and mechanism of action

- Both quinine and quinidine are derivatives from the park of cinchona tree. Quinidine is the D-isomer of quinine.
- Quinine is highly active **blood schizonticide** against the **four** species of human malaria parasites, but it is primarily used to treat **chloroquine-resistant *P. falciparum***, often in combination with **doxycycline**.
- The exact antimalarial mechanism is **unknown**.

Therapeutic uses: treatment of **chloroquine-resistant *P. falciparum***.

Adverse effects (more common with i.v. administration)

- **Cinchonism:** tinnitus, ringing in ears, blurred vision, headache, and vomiting.
- **CVS:** hypotension, **syncope**, cardiac arrhythmias and ↑ **QT** interval.
- **Hypoglycemia** is important and may be **fatal** side effect with i.v. administration. It is due to stimulation of insulin release).

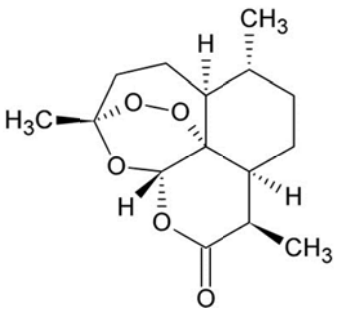
- **Blackwater fever (rare):** massive hemolysis with fever, hemoglobinurea, and dark urine. The pathogenesis is unclear.
- **Hemolysis** in G-6PD deficient persons.
- Hypersensitivity reactions.

N.B.

Although quinine causes **uterine contractions** but the WHO guidelines consider **pregnancy is NOT a contraindication of quinine.**

Artemisinin and its analogs

Structure and mechanism of action



- Artemisinin is the active component of a Chinese herb. The compound contains unusual **peroxide bridge**. Cleavage of this peroxide bridge inside the digestion vacuole liberates **oxygen free radicals** which are lethal to the parasite.
- Artemisinin and its analogs are very rapidly acting **blood schizonticides** against **all** human malaria parasites. They have no effect on hepatic stages.

Pharmacokinetics

- Artemisinin is insoluble and can be used **only orally**.
- **Artesunate** and **artemether** are semisynthetic analogs with improved solubility to be suitable for **parenteral** administration.

Therapeutic uses

- Combination of artemisinin and other antimalarials is now the standard treatment of **falciparum malaria** in nearly all endemic areas.
- **IV artesunate** is now recommended by the WHO in preference to IV quinine due to fewer side effects.

Adverse effects: GI disturbances and, rarely, allergic reactions and hemolysis.

Mefloquine

Structure and mechanism of action

- Mefloquine is structurally related to quinine.
- Strong **blood schizonticide** against *P. falciparum* by **unknown** mechanism.
- It is given **only orally** because parenteral administration causes severe irritation.

Therapeutic uses: treatment of chloroquine-resistant falciparum malaria.

Adverse effects: neurotoxicity: headache, vertigo, psychosis, and confusion.

Primaquine

Mechanism of action

Primaquine is a **hepatic schizonticide** (for *P. vivax and P. ovale*) and **gametocide** (in all 4 types of malaria), through an **unknown mechanism.**

Therapeutic uses

- **Radical cure:** after successful treatment, it is given orally for 15 days to kill the dormant hypnozoites in the liver and prevent **relapse**.
- **Causal prophylaxis:** but prolonged course of primaquine should be avoided.
- **Prevention of transmission:** by killing the gametocytes in all 4 types of malaria.

Adverse effects

– **Methemoglobinemia** nearly in **all** patients.
– **Severe hemolysis** in patients with G-6PD deficiency.
– GIT upset, visual disturbance, and leucopenia.

Antifolate drugs
(Pyrimethamine, Proguanil, Fansidar)

Mechanism of action: ↓ folic acid synthesis necessary for DNA synthesis.

Therapeutic uses

- **Fansidar** is a combination of sulfadoxine + pyrimethamine. It produces sequential block of folic acid synthesis. It is used to treat the acute attack of **chloroquine-resistant malaria** in combination with quinine or artemisinin.
- **Proguanil** is used for prophylaxis and for prevention of transmission.
- **Pyrimethamine** is used for clinical cure and for prevention of transmission.

Part 9: Anthelmintic Drugs

Helminths can be divided into three main groups:

Nematodes (round worms)	Trematodes (flukes)	Cestodes (tape worms)
Intestinal nematodes: *Ascaris lumbricoides* *Ankylostoma duodenale* *Enterobius vermicularis* *Trichuris trichiura* *Strongyloides stercoralis* *Trichostrongylus* **Tissue nematodes:** *Filaria.* *Guinea worm.* *Cutaneous and visceral Larva migrans.*	*Schistosomes* **Intestinal flukes:** *Heterophyes heterophyes* *Metagonimus yokogawia* *Fasciolopsis buski* **Liver flukes:** *Fasciola hepatica* **Lung flukes:** *Paragonimus westermani*	*Taenia saginata* *Taenia solium* *Diphyllobothrium latum* *Hymenolepis nana.* *Hydatid tape worm.*

DRUGS EFFECTIVE AGAINST NEMATODES

1. Benzimidazoles
[Albendazole – Mebendazole – Thiabendazole]

Mechanism of action

These agents inhibit **microtubule synthesis** and **glucose uptake** by the worms. The two effects lead to ↓ ATP production and paralysis of the worm.

Therapeutic uses

Benzimidazoles are broad-spectrum anthelmintic drugs.

- **For intestinal nematodes:** (400 mg once daily on an empty stomach for 2-3 days).
- **For tissue nematodes:** (400 mg twice daily with a fatty meal for 10 days).
- **For hydatid disease**: (400 mg twice daily for one month).
- **Neurocysticercosis:** albendazole is the drug of choice (400 mg twice daily with a fatty meal for 21 days). It is given with corticosteroids to minimize the immune reaction caused by the dying organisms.

Adverse effects: usually mild and mainly GIT upsets.

2. Pyrantel pamoate

- It causes depolarizing neuromuscular blockade and inhibits ChE enzyme in the parasite → paralysis of the worm.
- It is used for intraluminal round worms.
- **Adverse effects:** very few.

3. Diethylcarbamazine (Hetrazan)

- It causes paralysis of **microfilaria** and alters their surface structure, making them more susceptible to destruction by host defense mechanisms. The mechanism is **unknown.**
- **Therapeutic uses:** treatment of **filariasis** (Wucheraria bancrofti and Loa loa).
- **Adverse effects:** sudden death of the microfilaria can produce **severe allergic reactions** e.g. fever, leukocytosis, eosinophilia, edema, rashes, tachycardia and headache (**corticosteroid**s may be needed to suppress these allergic reactions).

DRUGS EFFECTIVE AGAINST TREMATODES AND CESTODES

1. Praziquantel

Mechanism of action

It increases cell membrane permeability of Ca^{2+}. This leads to rapid and prolonged muscle contraction and paralysis of the worm.

Therapeutic uses

- **Treatment of schistosomiasis:** it is active against adult worm and all immature forms in all species (40 mg/kg single dose orally).
- **Other flukes:** *e.g. H. heterophyes, Fasciolopsis buski, Paragonimus westermani.*
- **Cestodes:** *T. saginata, T. solium, D. latum, and H. nana.*

Adverse effects

- Nausea, vomiting, drowsiness, arthralgia, myalgia and low grade fever.
- Mild elevation of liver enzymes.

Contraindications and cautions:

Praziquantel is contraindicated in **ocular cysticercosis**, because parasite destruction in the eye may cause immune reaction and irreversible damage. Some workers also caution against use of the drug in **neurocysticercosis** for the same reason.

2. Bithinol

- It inhibits the parasite respiration.
- It is an alternative to triclabendazole for **Fasciola hepatica** (sheep liver fluke infection) and as an alternative to praziquantel for **pulmonary paragonimiasis**.

3. Niclosamide

- It is a second line drug for most tape worm (cestodes) infections.
- It appears to act by inhibition of oxidative phosphorylation and ↓ energy production.
- It is given as 2g once on an empty stomach.
- Adverse effects are minimal because the drug is not absorbed.

Infecting Organism	Drug of Choice	Alternative Drugs
Roundworms (nematodes)		
Ascaris lumbricoides (roundworm)	Albendazole or pyrantel pamoate	Ivermectin, piperazine
Trichuris trichiura (whipworm)	Mebendazole or albendazole	Ivermectin
Necator americanus (hookworm); *Ancylostoma duodenale* (hookworm)	Albendazole or mebendazole or pyrantel pamoate	
Strongyloides stercoralis (threadworm)	Ivermectin	Albendazole or thiabendazole
Enterobius vermicularis (pinworm)	Mebendazole or pyrantel pamoate	Albendazole
Trichinella spiralis (trichinosis)	Mebendazole or albendazole; add corticosteroids for severe infection	
Trichostrongylus species	Pyrantel pamoate or mebendazole	Albendazole
Cutaneous larva migrans (creeping eruption)	Albendazole or ivermectin	Thiabendazole (topical)
Visceral larva migrans	Albendazole	Mebendazole
Angiostrongylus cantonensis	Albendazole or mebendazole	
Wuchereria bancrofti (filariasis); *Brugia malayi* (filariasis); tropical eosinophilia; *Loa loa* (loiasis)	Diethylcarbamazine	Ivermectin
Onchocerca volvulus (onchocerciasis)	Ivermectin	
Dracunculus medinensis (guinea worm)	Metronidazole	Thiabendazole or mebendazole
Capillaria philippinensis (intestinal capillariasis)	Albendazole	Mebendazole
Flukes (trematodes)		
Schistosoma haematobium (bilharziasis)	Praziquantel	Metrifonate
Schistosoma mansoni	Praziquantel	Oxamniquine
Paragonimus westermani (lung fluke)	Praziquantel	Bithionol
Fasciola hepatica (sheep liver fluke)	Bithionol or triclabendazole	
Fasciolopsis buski (large intestinal fluke)	Praziquantel or niclosamide	
Heterophyes heterophyes; Metagonimus yokogawai (small intestinal flukes)	Praziquantel or niclosamide	
Tapeworms (cestodes)		
Taenia saginata (beef tapeworm)	Praziquantel or niclosamide	Mebendazole
Diphyllobothrium latum (fish tapeworm)	Praziquantel or niclosamide	
Taenia solium (pork tapeworm)	Praziquantel or niclosamide	
Cysticercosis (pork tapeworm larval stage)	Albendazole	Praziquantel
Hymenolepis nana (dwarf tapeworm)	Praziquantel	Niclosamide, nitazoxanide
Echinococcus granulosus (hydatid disease); *Echinococcus multilocularis*	Albendazole	

Notes

Clinical
Pharmacology
Department

Mansoura Faculty of Medicine

Review Questions

1. Mention the antibacterial mechanism of action and the major adverse effects of each of the following drugs:
   - Penicillin
   - Clarithromycin
   - Aminoglycosides
   - Tetracyclines
   - Vancomycin
   - Isoniazid
   - Ethambutol

2. Mention the antiviral mechanism of action and the major adverse effects of each of the following drugs:
   - Interferon-alpha
   - Acyclovir
   - Amantadine

3. Mention the antifungal mechanism of action and the major adverse effects of each of the following drugs:
   - Itraconazole
   - Amphotricin B

4. Mention the antiprorozoal mechanism of action and the major adverse effects of each of the following drugs:
   - Metronidazole
   - Chloroquine
   - Artemisinin

5. Give a short account on the drug management and drug(s) of best choice in the following infections:
   - Bacterial meningitis
   - Community-acquired pneumonia
   - Bites (human or animal)
   - Typhoid fever
   - Pseudomembranous colitis
   - Gonorrhea

6. Discuss drug treatment of hepatitis C virus. Mention the mechanism of action and major adverse effects of interferon-alpha.
7. Discuss drug treatment of amebic liver abscess. Mention the mechanism of each drug.
8. Discuss drug treatment of chloroquine-resistant *P. falciparum* malaria. Mention the mechanism and major adverse effects of each drug.

Of each of the following questions, select ONE BEST answer:

1. The penicillin G preparation with the longest duration of action is
A. Benzathine penicillin
B. Sodium penicillin
C. Potassium penicillin
D. Procaine penicillin
E. Pipracillin

2. If a patient gives history of urticaria, itching and swelling of lips following injection of penicillin G, then
A. He will develop milder reaction whenever penicillin is injected
B. He can be given ampicillin safely
C. He can be given cephalosporins safely
D. He can be given oral phenoxymethyl penicillin safely
E. All natural and semisynthetic penicillins are contraindicated for him

3. The most important reason for highly restricted use of penicillin G injections in present day therapeutics is its
A. Narrow spectrum of activity
B. Potential to cause hypersensitivity reaction
C. Short duration of action
D. Neurotoxicity
E. Nephrotoxicity

4. Cefotaxime act by the following mechanism:
A. Inhibition of bacterial protein synthesis
B. Inhibition of bacterial cell wall synthesis
C. Inhibition of bacterial nucleic acid synthesis
D. Inhibition of bacterial folic acid synthesis
E. Inhibition of bacterial cell division

5. Benzathine penicillin injected once every 4 weeks for 8 years or more is the drug of choice for
A. Agranulocytosis patients
B. Prophylaxis of bacterial endocarditis in patients with valvular defects
C. Prophylaxis of rheumatic fever
D. Treatment of anthrax
E. Treatment of sinusitis

6. Amoxicillin is inferior to ampicillin for the treatment of the following infection
A. Typhoid
B. Tonsilitis
C. Shigella enteritis
D. Subacute bacterial endocarditis
E. Gonorrhoea

7. Which one of the following statements about ampicillin is false?
A. Its activity is enhanced by sulbactam
B. It causes maculopapular rashes
C. It is the drug of choice for Listeria monocytogenes infection
D. It eradicates most strains of MRSA
E. Pseudomembranous colitis may occur with its use

8. The mechanism of antibacterial action of azithromycin involves
A. Binding to a component of the 50S ribosomal subunit
B. Inhibition of translocase activity
C. Blockade of binding of aminoacyl – tRNA to bacterial ribosomes
D. Selective inhibition of ribosomal peptidyl transferases
E. Inhibition of DNA–dependent RNA polymerase

9. In the empiric treatment of severe bacterial infections of unidentified etiology, this drug, often used in combination with an aminoglycoside, provides coverage against many staphylococci
A. Amoxicillin
B. Clavulanic acid
C. Erythromycin
D. Nafcillin
E. Tetracycline

10. *C. difficile* colitis is more common complication with the use of:
A. Cephalosporins
B. Vancomycin
C. Co-trimoxazole
D. Meropenem
E. Flucoloxacillin

11. Beta – lactamase production by strains of Haemophilus influenzae,

Moraxella catarrhalis, and Neissera gonorrhoeae confers resistance against penicillin G. which one of the following antibiotics is most likely to be effective against all strains of each of the above organisms?
A. Ampicillin
B. Ceftriaxone
C. Clindamycin
D. Erythromycin
E. Piperacillin

12. A 19-year-old woman with recurrent sinusitis has been treated with different antibiotics on several occasions. During the course of one such treatment she developed a severe diarrhea and was hospitalized. Sigmoidoscopy revealed colitis, and pseudomembranes, were confirmed histologically. Which of the following drugs, administered orally, is most likely to be effective in the treatment of colitis due to C difficile?
A. Ampicillin
B. Azithromycin
C. Clindamycin
D. Metonidazole
E. Tetracycline

13. The drug of choice for Lyme disease is:
A. Doxycycline
B. Sulfonamides
C. Penicillin
D. Erythromycin
E. Topramycin

14. The drug of choice for anaerobic infections is:
A. Tetracycline
B. Sulfonamides
C. Penicillin
D. Erythromycin
E. Metronidazole

15. The drug of choice for typhoid fever is:
A. Tetracycline
B. Sulfonamides
C. Penicillin G
D. Ciprofloxacin
E. Metronidazole

16. Methicillin resistant staphylococci do not respond to β-lactam antibiotics because
A. They produce a β-lactamase which destroys methicillin and related drugs
B. They elaborate an amidase which destroys methicillin and related drugs
C. They have acquired a penicillin binding protein which has low affinity for β-lactam antibiotics
D. They are less permeable to β-lactam antibiotics

17. Indicate the sulfonamide whose sodium salt yields a nearly neutral solution which is suitable for topical use in the eye
A. Sulfadiazine
B. Sulfacetamide
C. Sulfamerazine
D. Sulfamethizole

18. Which of the following is not true of sulfonamides?
A. They are primarily metabolized by acetylation
B. They are more likely to produce crystalluria in alkaline urine in which they are less soluble
C. They may exert bactericidal action in the urinary tract
D. Used alone, they have become therapeutically unreliable for serious infections

19. Clavulanic acid is combined with amoxicillin because
A. It kills bacteria that are not killed by amoxicillin
B. It reduces renal clearance of amoxicillin
C. It counteracts the adverse effects of amoxicillin
D. It inhibits beta lactamases that destroy amoxicillin

20. Which toxic effect of aminoglycoside antibiotics is most irreversible in nature?
A. Optic neuropathy
B. Ototoxicity
C. Hepatotoxicity
D. Muscle weakness
E. Kidney damage

21. Highest incidence of antibiotic associated pseudo membranous enterocolitis has been noted with the use of
A. Ampicillin
B. Chloramphenicol
C. Vancomycin
D. Clindamycin
E. Gentamycin

22. Which antibiotic class can cause teeth staining and dental enamel hypoplasia if given to small children?
A. Fluoroquinolones
B. Cephalosporins
C. Tetracyclines
D. Aminoglycosides
E. Macrolides

23. Antiviral agents that are active against cytomegalovirus (CMV) include which of the following?
A. Ganciclovir
B. Acyclovir
C. Amantadine
D. Oseltamivir
E. Ribavirin

24. Which one of the following drugs is least likely to be effective in the treatment of esophageal candidiasis, it is used by the oral route?
A. Amphotericin B
B. Clotrimazole
C. Fluconazole
D. Griseofulvin
E. Ketoconazole

25. Which one of the following drugs is most appropriate for oral use in vaginal candidiasis?
A. Clotrimazole
B. Griseofluvin
C. Fluconazole
D. Flucytosine
E. Nystatin

26. The antiviral actions of this drug include inhibition of both RNA and DNA synthesis. The drug is used for the treatment of severe respiratory syncytial virus infections in neonates.
A. Amantadine
B. Amprenavir
C. Oseltamivir
D. Ribavirin
E. Ritonavir

27. The primary mechanism of antibacterial action of penicillin involves inhibition of:
A. Beta-lactamases
B. Cell membrane synthesis
C. N-acetylmuramic acid synthesis
D. Peptidoglycan cross-linking
E. Transglycosylation

28. Fluid expressed from the penile chancre of a patient revealed to be infected with *Treponema pallidum*, the best course of action would be to:
A. Administer a single oral dose of fosfomycin
B. Administer a single oral dose of gentamycin
C. Inject intramuscular benzathine penicillin G
D. Treat with oral tetracycline for 7 d
E. Treat with vancomycin

29. Which of the following statements about beta-lactam antibiotics is false?
A. Cephalexin and other first-generation cephalosporins do not cross the blood-brain barrier
B. Ceftriaxone and nafcillin are both eliminated mainly via biliary secretion
C. Instability of penicillins in gastric acid can limit their oral absorption
D. Renal tubular reabsorption of amoxicillin is inhibited by probenecid
E. Ticarcillin has activity against several gram negative rods

30. A patient needs antibiotic treatment for native valve, culture positive infective enterococcal endocarditis. His medical history includes a severe anaphylactic reaction to penicillin G during the last year. The best approach would be treatment with
A. Amoxicillin-clavulanate
B. Aztreonam
C. Ceftriaxone
D. Ticarcillin
E. Vancomycin

31. If ampicillin and piperacillin are used in combination in the treatment of infections resulting from Pseudomonas aeruginosa, antagonism may occur. The most likely explanation is that

A. Ampicillin is bacteriostatic
B. Ampicillin induces beta-lactamase production
C. Autolytic enzymes are inhibited by piperacillin
D. Piperacillin blocks the attachment of ampicillin to penicillin-binding proteins
E. The 2 drugs form an insoluble complex

32. Which statement about vancomycin is accurate?

A. Active against methicillin-resistant staphylococci
B. Bacteriostatic
C. Binds to PBPs
D. Hepatic metabolism
E. Oral bioavailability

33. A 52 years old patient with signs and symptoms suggestive of typical bacterial meningitis. Treatment of this patient should be initiated immediately with intravenous administration of

A. Amoxicillin
B. Cephalexin
C. Benzylpenicillin G
D. Nafcillin
E. Piperacillin

34. The mechanism of antibacterial action of azithromycin involves:

A. Antagonism of bacterial translocase activity
B. Binding to a component of the 50S ribosomal subunit
C. Inhibition of DNA-dependent RNA polymerase
D. Interference with binding of aminoacyl-tRNA to bacterial ribosomes
E. Selective inhibition of ribosomal peptidyl transferases

35. If a patient had been scheduled for elective colonic surgery, optimal prophylaxis against infection would be achieved by the use of

A. Intravenous cefoxitin
B. Intravenous third-generation cephalosporin
C. Oral amoxicillin
D. Oral ciprofloxacin
E. Oral neomycin

36. Clarithromycin and erythromycin have very similar spectra of antimicrobial activity. The major advantage of clarithromycin is that it

A. Does not inhibit hepatic drug-metabolizing enzymes
B. Eradicates mycoplasmal infections in a single dose
C. Has greater activity against *H pylori*
D. Is active against methicillin-resistant strains of staphylococci
E. Is active against strains of streptococci that are resistant to erythromycin

37. The primary mechanism of resistance of gram-positive organisms to macrolide antibiotics including erythromycin is

A. Changes in the 30S ribosomal subunit
B. Decreased drug permeability of the cytoplasmic membrane
C. Formation of drug-inactivating acetyltransferases
D. Formation of esterases that hydrolyze the lactone ring
E. Methylation of binding sites on the 50S ribosomal subunit

38. A suitable treatment for community-acquired pneumonia with little risk of drug interactions can be achieved with

A. Azithromycin
B. Clindamycin
C. Doxycycline
D. Erythromycin
E. Vancomycin

39. Regarding the toxicity of aminoglycosides which statement is accurate?

A. Gentamicin and tobramycin rarely cause renal damage
B. Ototoxicity includes vestibular dysfunction, which may be irreversible
C. Ototoxicity is reduced if loop diuretics are used to facilitate the renal

excretion of aminoglycoside antibiotics
D. Reduced blood creatinine is an early sign of aminoglycoside nephrotoxicity
E. Skin reactions are very rare following topical use of neomycin

40. Your 23-year-old female patient is pregnant and has gonorrhea. The medical history includes anaphylaxis following exposure to amoxicillin. The most appropriate drug to use is
A. Azithromycin
B. Cefixime
C. Ceftriaxone
D. Ciprofloxacin
E. Doxycycline

41. In a patient suffering from pseudomembranous colitis due to C difficile with established hypersensitivity to metronidazole the most likely drug to be of clinical value is
A. Amoxicillin
B. Chloramphenicol
C. Doxycycline
D. Levofloxacin
E. Vancomycin

42. Trimethoprim-sulfamethoxazole is established to be effective against which of the following opportunistic infections in the AIDS patient?
A. Cryptococcal meningitis
B. Herpes simplex
C. Oral candidiasis
D. Toxoplasmosis
E. Tuberculosis

43. A 65-year-old woman has returned from a vacation abroad suffering from traveler's diarrhea, and her problem has not responded to antidiarrheal drugs. A pathogenic gram-negative bacillus is suspected. Which drug is most likely to be effective in the treatment of this patient?
A. Ampicillin
B. Ciprofloxacin
C. Sulfadiazine
D. Trimethoprim
E. Vancomycin

44. Silver sulfadiazine is clinically used for:
A. Treatment of Rocky Mountain spotted fever
B. To prevent infections of skin burns
C. Treatment of typhoid fever
D. Treatment of Legionella pneumonia
E. Treatment of lead toxicity

45. Which statement about the fluoroquinolones is accurate?
A. Antacids increase their oral bioavailability
B. Contraindicated in patients with hepatic dysfunction
C. Fluoroquinolones are drugs of choice in a 6-year-old child with a urinary tract
D. Gonococcal resistance to fluoroquinolones may involve changes in DNA gyrase
E. Modification of dosage is required in patients renal impairment.

46. Which adverse effect is most common with sulfonamides?
A. Stevens Johnson syndrome
B. Hematuria
C. Kernicterus in the newborn
D. Neurologic dysfunction
E. Skin rash

47. Which statement about ciprofloxacin is accurate?
A. Antagonism occurs if used with dihydrofolate reductase inhibitors
B. Ciprofloxacin is active against MRSA strains of staphylococci
C. Most "first-time" urinary tract infections are resistant to ciprofloxacin
D. Organisms that commonly cause ear infections are highly resistant
E. Tendinitis may occur during treatment

48. Supplementary folinic acid may prevent anemia in folate-deficient persons who use this drug
A. Ciprofloxacin
B. Levofloxacin
C. Linezolid
D. Clarithromycin
E. Trimethoprim

49. Supplementary pyridoxin may prevent neurotoxicity in persons who use this drug
A. Ciprofloxacin
B. Isoniazid
C. Linezolid
D. Clarithromycin
E. Trimethoprim

50. Which statement regarding ethambutol is correct?
A. It is contraindicated in pregnancy
B. Visual adverse effects are very rare
C. It inhibits arabinosyl transferase involved in cell wall biosynthesis
D. Ocular toxicity of ethambutol is prevented by thiamine
E. Resistance is common and rapid.

51. Interactions between this drug and cell membrane components can result in the formation of pores lined by hydrophilic groups present in the drug molecule.
A. Caspofungin
B. Flucytosine
C. Griseofulvin
D. Nystatin
E. Terbinafine

52. Which statement about fluconazole is accurate?
A. Does not penetrate the blood-brain barrier
B. Drug of choice in treatment of aspergillosis
C. Induces hepatic drug-metabolizing enzymes
D. Has the least effect of all azoles on drug metabolism
E. Oral bioavailability is less than that of ketoconazole

53. The following is the drug of choice for invasive aspergillosis
A. Voriconazole
B. Ketoconazole
C. Miconazole
D. Fluconazole
E. Itraconazole

54. The drug most likely to suppress herpetic infections and provide prophylaxis against CMV retinitis in AIDS patient is
A. Fluconazole
B. Gancyclovir
C. Indinavir
D. Rifabutin
E. Trimethoprim-sulfamethoxazole

55. Which of the following statements about interferon-alpha is false?
A. At the start of treatment, most patients experience flu-like symptoms
B. Therapeutic outcome is low when used alone for HCV
C. It is used in the management of hepatitis B and C
D. Lamivudine interferes with its activity against hepatitis B
E. Toxicity includes bone marrow suppression

56. A 22-year-old man with gonorrhea is to be treated with cefixime and will need another drug to provide coverage for possible urethritis caused by *Clmydia trachomatis.* Which of the following drugs is least likely to be effective in non-gonococcal urethritis?
A. Azithromycin
B. Ciprofloxacin
C. Co-trimoxazole
D. Nitrofurantoin
E. Tetracycline

57. The drug regimen most likely to be effective in treating severe extraintestinal amebiasis is
A. Chloroquine
B. Diloxanide furoate plus iodoquinol
C. Emetine plus diloxanide furoate plus chloroquine
D. Chloroquine followed by primaquine
E. Tinidazole plus diloxanide furoate

58. Metronidazole is not effective in the treatment of
A. Amebiasis
B. Infections due to *Bacteroides fragilis*
C. Infections due to *Pneumocystis carinii*
D. Pseudomembranous colitis
E. Trichomoniasis

59. Which statement about antiprotozoal drugs is accurate?

A. Chloroquine is an inhibitor of plasmodial dihydrofolate reductase
B. Mefloquine destroys secondary exoerythrocytic schizonts
C. Primaquine is a blood schizonticide and does not affect secondary tissue schizonts
D. Artemisinin is not useful for *P. falciparum* malaria
E. Intravenous quinine can cause serious arrhythmia

60. Plasmodial resistance to chloroquine is due to:
A. Change in receptor structure
B. Decreased accumulation of the drug in the food vacuole
C. Increased activity of DNA repair mechanisms
D. Increased synthesis of dihydrofolate reductase
E. Induction of drug-inactivating enzymes

61. Which drug should be used for treatment of the acute attack of *P vivax* malaria but does not eradicate exoerythrocytic forms of the parasite?
A. Chloroquine
B. Mefloquine
C. Primaquine
D. Pyrimethamine-sulfadoxine
E. Quinidine

62. After successful treatment of malaria, which drug should be given later to eradicate schizonts and latent hypnozoites in the patient's liver?
A. Artesunate
B. Fansidar (Pyrimethamine-sulfadoxine)
C. Chloroquine
D. Primaquine
E. Quinine

Answers

1 A	14 E	27 D	40 A	53 A
2 E	15 D	28 C	41 E	54 B
3 A	16 A	29 D	42 D	55 D
4 B	17 B	30 E	43 B	56 D
5 C	18 B	31 E	44 B	57 E
6 C	19 D	32 A	45 D	58 C
7 D	20 B	33 C	46 E	59 E
8 A	21 D	34 B	47 E	60 B
9 D	22 C	35 E	48 E	61 A
10 A	23 A	36 C	49 B	62 D
11 B	24 D	37 E	50 C	
12 D	25 C	38 A	51 D	
13 A	26 D	39 B	52 D	